```
=> b reg
FILE 'REGISTRY' ENTERED AT 14:43:45 ON 21 JUN 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   20 JUN 2005  HIGHEST RN 852602-49-4
DICTIONARY FILE UPDATES:  20 JUN 2005  HIGHEST RN 852602-49-4

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

**********************************************************************
*                                                                    *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,    *
* effective March 20, 2005.  A new display format, IDERL, is now     *
* available and contains the CA role and document type information.  *
*                                                                    *
**********************************************************************

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> d ide l7 tot

L7   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   9046-27-9  REGISTRY
ED   Entered STN:  16 Nov 1984
CN   Glutamyltransferase, γ- (9CI)   (CA INDEX NAME)
OTHER NAMES:
CN   α-Glutamyltranspeptidase
CN   γ-Glutamyl peptidyltransferase
CN   γ-Glutamyl transpeptidase
CN   γ-Glutamyl transpeptidase-related enzyme
CN   γ-Glutamyltransferase
CN   γ-GPT
CN   γ-GT
CN   γ-GTP
CN   E.C. 2.3.2.2
CN   L-γ-Glutamyl transpeptidase
CN   L-γ-Glutamyltransferase
CN   L-Glutamyltransferase
DR   9013-62-1
MF   Unspecified
CI   MAN
LC   STN Files:   ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, CA, CABA,
       CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CSCHEM, CSNB, IFICDB, IFIPAT,
       IFIUDB, MSDS-OHS, NAPRALERT, NIOSHTIC, PROMT, TOXCENTER, USPAT2,
       USPATFULL
     Other Sources:   EINECS**, TSCA**
         (**Enter CHEMLIST File for up-to-date regulatory information)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
            8426 REFERENCES IN FILE CA (1907 TO DATE)
```
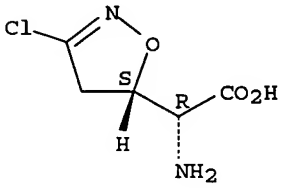

14 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
8438 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> d ide l10 tot

L10 ANSWER 1 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN
RN 676551-24-9 REGISTRY
ED Entered STN: 23 Apr 2004
CN 5-Isoxazoleacetic acid, α-amino-3-chloro-4,5-dihydro-, (αR,5S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C5 H7 Cl N2 O3
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

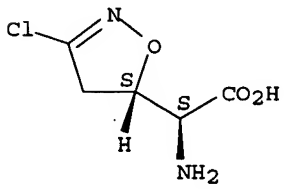


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L10 ANSWER 2 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN
RN 161922-40-3 REGISTRY
ED Entered STN: 04 Apr 1995
CN 5-Isoxazoleacetic acid, α-amino-3-chloro-4,5-dihydro-, monohydrochloride, [S-(R*,R*)]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C5 H7 Cl N2 O3 . Cl H
SR CA
LC STN Files: CA, CAPLUS
CRN (42228-92-2)

Absolute stereochemistry.



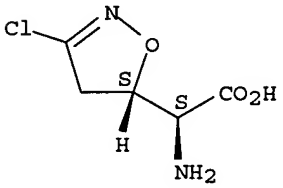
● HCl

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L10 ANSWER 3 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN
RN 105116-13-0 REGISTRY
ED Entered STN: 08 Nov 1986

CN 5-Isoxazoleacetic acid, α-amino-3-chloro-4,5-dihydro-, monohydrochloride, (R*,R*)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 5-Isoxazoleacetic acid, α-amino-3-chloro-4,5-dihydro-, monohydrochloride, (R*,R*)-(±)-
FS STEREOSEARCH
MF **C5 H7 Cl N2 O3 . Cl H**
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, TOXCENTER
(*File contains numerically searchable property data)
CRN (76898-56-1)

Relative stereochemistry.

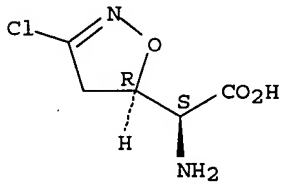


● HCl

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L10 ANSWER 4 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN
RN 104832-77-1 REGISTRY
ED Entered STN: 25 Oct 1986
CN 5-Isoxazoleacetic acid, α-amino-3-chloro-4,5-dihydro-, (R*,S*)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 5-Isoxazoleacetic acid, α-amino-3-chloro-4,5-dihydro-, (R*,S*)-(±)-
FS STEREOSEARCH
MF **C5 H7 Cl N2 O3**
CI COM
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)

Relative stereochemistry.



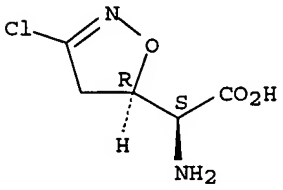
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L10 ANSWER 5 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN
RN 104832-76-0 REGISTRY
ED Entered STN: 25 Oct 1986

CN 5-Isoxazoleacetic acid, α-amino-3-chloro-4,5-dihydro-, monohydrochloride, (R*,S*)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 5-Isoxazoleacetic acid, α-amino-3-chloro-4,5-dihydro-, monohydrochloride, (R*,S*)-(±)-
FS STEREOSEARCH
MF **C5 H7 Cl N2 O3 . Cl H**
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, TOXCENTER
(*File contains numerically searchable property data)
CRN (104832-77-1)

Relative stereochemistry.

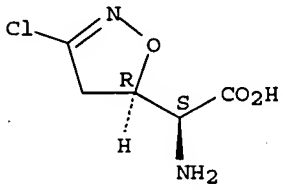


● HCl

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L10 ANSWER 6 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN
RN 80184-13-0 REGISTRY
ED Entered STN: 16 Nov 1984
CN 5-Isoxazoleacetic acid, α-amino-3-chloro-4,5-dihydro-, (αS,5R)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 5-Isoxazoleacetic acid, α-amino-3-chloro-4,5-dihydro-, [R-(R*,S*)]-
FS STEREOSEARCH
MF **C5 H7 Cl N2 O3**
LC STN Files: BEILSTEIN*, CA, CAPLUS, TOXCENTER
(*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (-).



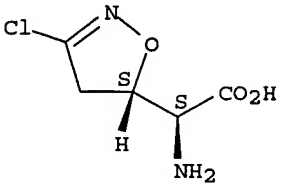
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L10 ANSWER 7 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN
RN 76898-56-1 REGISTRY
ED Entered STN: 16 Nov 1984
CN 5-Isoxazoleacetic acid, α-amino-3-chloro-4,5-dihydro-, (R*,R*)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:

CN 5-Isoxazoleacetic acid, α-amino-3-chloro-4,5-dihydro-, (R*,R*)-(±)-
OTHER NAMES:
CN (±)-Acivicin
FS STEREOSEARCH
MF **C5 H7 Cl N2 O3**
CI COM
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)

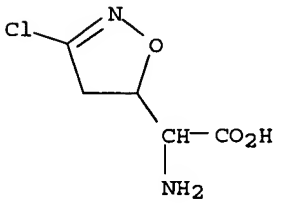
Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L10 ANSWER 8 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN
RN 52583-41-2 REGISTRY
ED Entered STN: 16 Nov 1984
CN 5-Isoxazoleacetic acid, α-amino-3-chloro-4,5-dihydro- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF **C5 H7 Cl N2 O3**
LC STN Files: BEILSTEIN*, CA, CANCERLIT, CAPLUS, MEDLINE, NIOSHTIC, TOXCENTER
(*File contains numerically searchable property data)



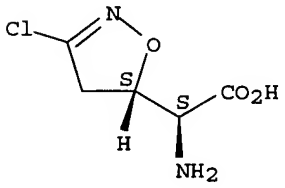
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L10 ANSWER 9 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN
RN 42228-92-2 REGISTRY
ED Entered STN: 16 Nov 1984
CN 5-Isoxazoleacetic acid, α-amino-3-chloro-4,5-dihydro-, (αS,5S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 5-Isoxazoleacetic acid, α-amino-3-chloro-4,5-dihydro-, [S-(R*,R*)]-
OTHER NAMES:
CN (α-S, 5S)-α-Amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid
CN Acivicin
CN Antibiotic AT 125

CN AT 125
CN NSC 163501
CN U 42126
FS STEREOSEARCH
MF C5 H7 Cl N2 O3
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CHEMCATS, CSCHEM, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MSDS-OHS, NAPRALERT, NIOSHTIC, PHAR, PROMT, PROUSDDR, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO

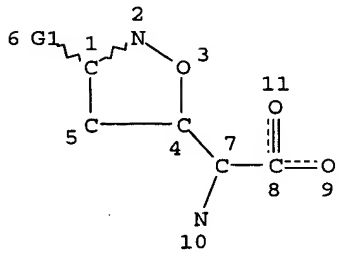
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

302 REFERENCES IN FILE CA (1907 TO DATE)
13 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
302 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> d que sta l15
L13 STR



VAR G1=O/X
NODE ATTRIBUTES:
NSPEC IS RC AT 10
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 11

STEREO ATTRIBUTES: NONE
L15 119 SEA FILE=REGISTRY SSS FUL L13

100.0% PROCESSED 209 ITERATIONS 119 ANSWERS
SEARCH TIME: 00.00.01

Search done by Noble Jarrell

```
=> d his full

     (FILE 'HOME' ENTERED AT 13:08:51 ON 21 JUN 2005)

     FILE 'HCAPLUS' ENTERED AT 13:57:10 ON 21 JUN 2005
L1             1 SEA ABB=ON  PLU=ON  US20040115284/PN OR (EP2000-107406# OR
                 WO2002-EP1799#)/AP,PRN

     FILE 'REGISTRY' ENTERED AT 13:58:13 ON 21 JUN 2005

     FILE 'HCAPLUS' ENTERED AT 13:58:16 ON 21 JUN 2005
L2             TRA L1 1- RN :       35 TERMS

     FILE 'REGISTRY' ENTERED AT 13:58:16 ON 21 JUN 2005
L3            35 SEA ABB=ON  PLU=ON  L2

     FILE 'WPIX' ENTERED AT 13:58:18 ON 21 JUN 2005
L4             2 SEA ABB=ON  PLU=ON  US20040115284/PN OR (EP2000-107406# OR
                 WO2002-EP1799#)/AP,PRN

     FILE 'REGISTRY' ENTERED AT 14:19:59 ON 21 JUN 2005
L5             1 SEA ABB=ON  PLU=ON  L3 AND ACIVICIN#
L6             2 SEA ABB=ON  PLU=ON  L3 AND GAMMA
L7             1 SEA ABB=ON  PLU=ON  L6 AND ?TRANSFER?/CNS
L8           494 SEA ABB=ON  PLU=ON  (GAMMA (1A)(GT# OR GLUTAMYLPEPTIDAS? OR
                 GLUTAMYLTRANSFERAS? OR GLUTAMYL (1A) (?PEPTIDAS? OR ?TRANSFERAS
                 E?)))/CNS
L9            11 SEA ABB=ON  PLU=ON  C5H7CLN2O3 AND NOC3/ES
L10            9 SEA ABB=ON  PLU=ON  L9 NOT (ACETAMIDE OR COMPD OR COMPOUND)
L11              STR
L12            6 SEA SSS SAM L11
L13              STR L11
L14            8 SEA SSS SAM L13
L15          119 SEA SSS FUL L13
                 SAV TEM HAR325F0/A L15

     FILE 'HCAPLUS' ENTERED AT 14:48:05 ON 21 JUN 2005
L16        14574 SEA ABB=ON  PLU=ON  (L7 OR L8)
L17        15976 SEA ABB=ON  PLU=ON  GLUTAMYLTRANSFERAS? OR GLUTAMYLPEPTIDAS?
                 OR GLUTAMYLTRANSPEPTIDAS? OR GAMMA (1A) (GT# OR GPT OR GLUTAM?
                 (1A)(?PEPTIDAS? OR ?TRANSFERAS?)) OR "EC2.3.2.2" OR "E.C.2.3.2.
                 2" OR (EC OR E(1A)C) (1A)"2.3.2.2"
L18          307 SEA ABB=ON  PLU=ON  L10 OR L10/D
L19          502 SEA ABB=ON  PLU=ON  ISOXZOLACET?(1A) ACID (1A)AMINO(1A)CHLORO
                 (2A)(DIHYDRO OR DI (1A)HYDRO) OR ACIVICIN# OR AT125 OR
                 AT(1A)125 OR NSC163501 OR NSC(1A)(163501 OR 163(1A)501) OR
                 U42126 OR U(1A)(42126 OR 42(1A)126)
L20          349 SEA ABB=ON  PLU=ON  L15
                 E CHRONIC RENAL DISEASE/CT
                 E E3+ALL
                 E KIDENY, DISEASE/CT
                 E KIDNEY, DISEASE/CT
                 E E3+ALL
L21         6301 SEA ABB=ON  PLU=ON  "KIDNEY, DISEASE"+OLD,NT/CT (L)CHRONIC?
                 E GLOMERULOSCL/CT
                 E E5+ALL
L22         1409 SEA ABB=ON  PLU=ON  "KIDNEY, DISEASE"+OLD,NT/CT (L) ?GLOMERULOS
                 CLER?

     FILE 'REGISTRY' ENTERED AT 15:05:48 ON 21 JUN 2005
L23            2 SEA ABB=ON  PLU=ON  L3 AND OXYGEN

     FILE 'HCAPLUS' ENTERED AT 15:06:26 ON 21 JUN 2005
                 E WEIHER H/AU
L24           32 SEA ABB=ON  PLU=ON  ("WEIHER H"/AU OR "WEIHER HANS"/AU)
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                E SIES H/AU
L25          826 SEA ABB=ON  PLU=ON  ("SIES H"/AU OR "SIES HELMUT"/AU)
                E WAGNER G/AU
L26         1692 SEA ABB=ON  PLU=ON  ("WAGNER G"/AU OR "WAGNER G A"/AU OR
                "WAGNER G A II"/AU OR "WAGNER G A III"/AU OR "WAGNER G B"/AU
                OR "WAGNER G C"/AU OR "WAGNER G CHRIST"/AU OR "WAGNER G D"/AU
                OR "WAGNER G D JR"/AU OR "WAGNER G DONALD"/AU OR "WAGNER G
                E"/AU OR "WAGNER G E JR"/AU OR "WAGNER G F"/AU OR "WAGNER G
                G"/AU OR "WAGNER G GALE"/AU OR "WAGNER G H"/AU OR "WAGNER G
                J"/AU OR "WAGNER G L"/AU OR "WAGNER G LOUIS"/AU OR "WAGNER G
                M"/AU OR "WAGNER G N"/AU OR "WAGNER G P"/AU OR "WAGNER G R"/AU
                OR "WAGNER G S"/AU OR "WAGNER G W"/AU)
                E WAGNER GUNTER/AU
L27          104 SEA ABB=ON  PLU=ON  ("WAGNER GUNTER"/AU OR "WAGNER GUNTER
                P"/AU OR "WAGNER GUNTHER"/AU OR "WAGNER GUNTHER A"/AU OR
                "WAGNER GUNTHER W"/AU)
L28            1 SEA ABB=ON  PLU=ON  (GTX (1A) PHARM?)/CS,PA
L29            5 SEA ABB=ON  PLU=ON  (L16 OR L17) AND L22
L30           27 SEA ABB=ON  PLU=ON  (L16 OR L17) AND L21
L31            2 SEA ABB=ON  PLU=ON  (L29 OR L30) AND (L24 OR L25 OR L26 OR L27
                OR L28)
L32            3 SEA ABB=ON  PLU=ON  L29 NOT L31
L33            0 SEA ABB=ON  PLU=ON  L32 AND (L18 OR L19 OR L20)
L34           25 SEA ABB=ON  PLU=ON  L30 NOT (L29 OR L31)
L35            0 SEA ABB=ON  PLU=ON  L34 AND (L18 OR L19 OR L20)
                E NEPROSIS/CT
                E NEPHROSIS/CT
                E E3+ALL
L36          421 SEA ABB=ON  PLU=ON  "KIDNEY, DISEASE"+OLD,NT/CT AND (L16 OR
                L17)
L37           11 SEA ABB=ON  PLU=ON  L36 AND (L18 OR L19 OR L20)
L38            2 SEA ABB=ON  PLU=ON  L37 AND (L24 OR L25 OR L26 OR L27 OR L28)
L39            9 SEA ABB=ON  PLU=ON  L37 NOT L38
L40         5729 SEA ABB=ON  PLU=ON  (L16 OR L17) (L) (INHIB? OR BLOCK? OR
                ANTAGON?)
L41         2417 SEA ABB=ON  PLU=ON  GGT
L42          377 SEA ABB=ON  PLU=ON  L41 (L) (INHIB? OR BLOCK? OR ANTAGON?)
L43           57 SEA ABB=ON  PLU=ON  (L41 OR L42) AND (L21 OR L22 OR "KIDNEY,
                DISEASE"+OLD,NT/CT)
L44            2 SEA ABB=ON  PLU=ON  L43 AND (L18 OR L19 OR L20)
L45            1 SEA ABB=ON  PLU=ON  L44 AND (L24 OR L25 OR L26 OR L27 OR L28)
L46            1 SEA ABB=ON  PLU=ON  L44 NOT L45
L47              QUE ABB=ON  PLU=ON  PY<=2001 OR AY<2001 OR AY<=2001 OR
                PD<20010220 OR AD<20010220 OR PRD<20010220
L48            4 SEA ABB=ON  PLU=ON  L32 OR L46
L49            3 SEA ABB=ON  PLU=ON  L48 AND L47
L50            4 SEA ABB=ON  PLU=ON  (L48 OR L49)
L51            2 SEA ABB=ON  PLU=ON  L34 AND L40
L52              QUE ABB=ON  PLU=ON  REACT? (1A) (OXYGEN OR O2)
L53          159 SEA ABB=ON  PLU=ON  (L21 OR L22) AND L52
                E REACTIVE OXYGEN/CT
                E E4+ALL
L54        24862 SEA ABB=ON  PLU=ON  REACTIVE OXYGEN SPECIES/CT
L55          130 SEA ABB=ON  PLU=ON  (L21 OR L22) AND L54
L56            2 SEA ABB=ON  PLU=ON  (L53 OR L55) AND (L16 OR L17 OR L40 OR
                L42)
L57            2 SEA ABB=ON  PLU=ON  (L53 OR L55) AND (L18 OR L19 OR L20)
L58            2 SEA ABB=ON  PLU=ON  L56 AND (L18 OR L19 OR L20)
L59            2 SEA ABB=ON  PLU=ON  (L56 OR L57 OR L58) AND (L24 OR L25 OR L26
                OR L27 OR L28)
                E GUMERULOPATH/CT
                E GLUMERULOPATH/CT
                E GLOMERULOPATH/CT
                E E3+ALL
                E E4+ALL
L60              QUE ABB=ON  PLU=ON  "KIDNEY, DISEASE"+OLD,NT/CT
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L61        9392 SEA ABB=ON  PLU=ON  L60 (L)?GLOMERUL?
                E NEUROPATHY/CT
                E E3+ALL
                E NERVE, DISEASE/CT
                E E3+ALL
L62        2308 SEA ABB=ON  PLU=ON  "NERVE, DISEASE"+OLD,NT/CT (L)NEUROP? (L)
                ?DIABET?
L63          48 SEA ABB=ON  PLU=ON  (L61 OR L62) AND (L16 OR L17 OR L40 OR
                L42)
L64           2 SEA ABB=ON  PLU=ON  L63 AND (L18 OR L19 OR L20)
L65           2 SEA ABB=ON  PLU=ON  L64 AND (L24 OR L25 OR L26 OR L27 OR L28)
L66         278 SEA ABB=ON  PLU=ON  (L16 OR L17 OR L40 OR L42) AND (L18 OR L19
                OR L20)
                E DISEASES/CT
                E E3+ALL
                E E2
                E E3+OLD,NT1
L67       37301 SEA ABB=ON  PLU=ON  ("DISEASE, ANIMAL"+OLD,NT1/CT OR DISEASE?/C
                W)(L) (CHRONIC? OR ?DEGEN?)
L68           2 SEA ABB=ON  PLU=ON  L66 AND L67
L69           1 SEA ABB=ON  PLU=ON  L68 AND (L24 OR L25 OR L26 OR L27 OR L28)
L70           1 SEA ABB=ON  PLU=ON  L68 NOT L69
L71          23 SEA ABB=ON  PLU=ON  ("DISEASE, ANIMAL"+OLD,NT1/CT OR DISEASE?/C
                W) AND L66
L72           2 SEA ABB=ON  PLU=ON  L71 AND (L24 OR L25 OR L26 OR L27 OR L28)
L73          21 SEA ABB=ON  PLU=ON  L71 NOT L72
L74          14 SEA ABB=ON  PLU=ON  L73 AND L47
L75           3 SEA ABB=ON  PLU=ON  (L18 OR L19 OR L20) (L) (PAC OR THU OR
                BIOL+NT)/RL AND L74
L76           2 SEA ABB=ON  PLU=ON  L31 OR L38 OR L45 OR L59 OR L65 OR L69 OR
                L72
L77           9 SEA ABB=ON  PLU=ON  L50 OR L51 OR L75

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L76  ANSWER 1 OF 2  HCAPLUS  COPYRIGHT 2005 ACS on STN
AN   2002:657961  HCAPLUS
DN   137:195608
ED   Entered STN:  30 Aug 2002
TI   Use of γ -glutamyl transpeptidase (.
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gamma.-GT) inhibitors for the treatment of degenerative diseases
IN Weiher, Hans; Sies, Helmut; Wagner, Gunter
PA GTX Pharmaceuticals G.m.b.H., Germany
SO PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K038-06
ICS A61P027-16; A61P013-00
CC 1-12 (Pharmacology)
Section cross-reference(s): 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002066047	A1	20020829	WO 2002-EP1799	20020220
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	EP 1361885	A1	20031119	EP 2002-718150	20020220
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	US 2004115284	A1	20040617	US 2003-644325	20030819
PRAI	EP 2001-104063	A	20010220		
	EP 2000-107406	A	20010220		
	WO 2002-EP1799	W	20020220		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2002066047	ICM	A61K038-06
	ICS	A61P027-16; A61P013-00
WO 2002066047	ECLA	A61K038/06A
US 2004115284	NCL	424/649.000; 514/037.000; 514/012.000; 514/018.000; 514/064.000; 514/457.000
	ECLA	A61K031/704; A61K038/06

AB The invention discloses the use of γ -GT inhibitors for the preparation of a pharmaceutical composition for the treatment of a degenerative disease, in particular of chronic renal diseases or inner ear degenerative diseases.
ST degenerative disease treatment gamma glutamyl transpeptidase inhibitor; chronic renal disease treatment gamma glutamyl transpeptidase inhibitor; ear degenerative disease treatment gamma glutamyl transpeptidase inhibitor
IT Glycosides
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(amino, sensorineural deafness induced by; γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)
IT Kidney, disease
(chronic; γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)
IT Disease, animal
(degenerative; γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)
IT Kidney, disease
(diabetic nephropathy; γ -glutamyl

transpeptidase inhibitors for treatment of degenerative diseases)

IT Kidney, disease
(focal glomerulosclerosis; γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)

IT Kidney, disease
(glomerulosclerosis, segmental; γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)

IT Kidney, disease
(glomerulus, autoimmune; γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)

IT Kidney, disease
(glomerulus, inflammatory; γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)

IT Anti-inflammatory agents
Inflammation
(inflammatory glomerulonephropathy; γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)

IT Ear
(inner, degenerative condition or injury; γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)

IT Kidney, disease
(minimal change nephrosis; γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)

IT Peptides, biological studies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oligopeptides; γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)

IT Ear, disease
(otosclerosis; γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)

IT Aging, animal
Drugs
Metabolism
Physiology, animal
(sensorineural deafness induced by; γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)

IT Deafness
(sensorineural; γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)

IT Antioxidants
Drug delivery systems
Fibroblast
Peptidomimetics
(γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)

IT Reactive oxygen species
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)

IT Anilides
Peptides, biological studies
Proteins
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)
IT 70-18-8D, Glutathione, analogs
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(peptidomimetic; γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)
IT 15663-27-1D, Cisplatin, derivs.
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(sensorineural deafness induced by; γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)
IT 453650-49-2 453650-50-5 453650-51-6 453650-52-7 453650-53-8
453650-54-9 453650-55-0 453650-56-1 453650-57-2 453650-58-3
453650-59-4 453650-60-7 453650-61-8 453650-63-0 453650-64-1
453650-65-2 453650-66-3 453650-67-4 453650-68-5 453650-69-6
453650-70-9 453650-71-0
RL: PRP (Properties)
(unclaimed sequence; use of γ -glutamyl transpeptidase (γ -GT) inhibitors for the treatment of degenerative diseases)
IT 70-18-8, Glutathione, biological studies 7782-44-7D, Oxygen, reactive species 9001-05-2, Catalase 9001-48-3, GSSG reductase 9013-66-5, Glutathione peroxidase 9046-27-9, γ -Glutamyl transpeptidase 9054-89-1, Superoxide dismutase 11062-77-4, Superoxide 50812-37-8, Glutathione transferase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)
IT 42228-92-2, Acivicin 42228-92-2D, Acivicin, derivs. 72669-53-5 334700-46-8 334700-46-8D, derivs.
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)
RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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IT 9046-27-9, γ -Glutamyl transpeptidase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(γ -glutamyl transpeptidase inhibitors for treatment of degenerative diseases)
RN 9046-27-9 HCAPLUS
CN Glutamyltransferase, γ- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L76 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:699555 HCAPLUS

DN 136:4208
ED Entered STN: 26 Sep 2001
TI Enhanced **gamma-glutamyl transpeptidase** expression and superoxide production in Mpv17-/- glomerulosclerosis mice
AU **Wagner, Gunter**; Stettmaier, Kurt; Bors, Wolf; **Sies, Helmut**; Wagner, Eva-Maria; Reuter, Alexander; **Weiher, Hans**
CS Institut fur Physiologische Chemie I, Heinrich-Heine-Universitat, Dusseldorf, D-40001, Germany
SO Biological Chemistry (2001), 382(7), 1019-1025 July.
CODEN: BICHF3; ISSN: 1431-6730
PB Walter de Gruyter GmbH & Co. KG
DT Journal
LA English
CC 14-12 (Mammalian Pathological Biochemistry)
AB Recently, γ -**glutamyl transpeptidase**, which initiates cleavage of extracellular glutathione, has been shown to promote oxidative damage to cells. Here the authors examined a murine disease model of glomerulosclerosis, involving loss of the Mpv17 gene coding for a peroxisomal protein. In Mpv17-/- cells, enzyme activity and mRNA expression (examined by quant. RT-PCR) of membrane-bound .**gamma** .-**glutamyl transpeptidase** were increased, while plasma glutathione peroxidase and superoxide dismutase levels were lowered. Superoxide anion production in these cells was increased as documented by ESR spectroscopy. In the presence of Mn(III)tetrakis(4-benzoic acid)porphyrin, the activities of γ -**glutamyl transpeptidase** and plasma glutathione peroxidase were unchanged, suggesting a relationship between enzyme expression and the amount of reactive O species. **Inhibition** of γ -**glutamyl transpeptidase** by **acivicin** reverted the lowered plasma glutathione peroxidase and superoxide dismutase activities, indicating reciprocal control of gene expression for these enzymes.
ST gammaglutamyl transpeptidase superoxide glomerulosclerosis mouse model; glutathione peroxidase **reactive oxygen** species glomerulosclerosis; superoxide dismutase **reactive oxygen** species glomerulosclerosis
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**GGT**; γ -**glutamyl transpeptidase** expression and superoxide production in Mpv17-/- glomerulosclerosis murine model)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(GPx; γ -**glutamyl transpeptidase** expression and superoxide production in Mpv17-/- glomerulosclerosis murine model)
IT **Kidney, disease**
(**glomerulosclerosis**; enhanced γ -**glutamyl transpeptidase** expression and superoxide production in Mpv17-/- **glomerulosclerosis** mice)
IT **Disease** models
Human
(γ -**glutamyl transpeptidase** expression and superoxide production in Mpv17-/- glomerulosclerosis murine model)
IT Transcriptional regulation
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(γ -**glutamyl transpeptidase**, glutathione peroxidase, and superoxide dismutase, reciprocal control of gene expression in Mpv17-/- glomerulosclerosis murine model)
IT **Reactive oxygen species**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(γ -**glutamyl transpeptidase**, superoxide production, and **reactive oxygen** species in Mpv17-/- glomerulosclerosis murine model)
IT **9046-27-9**, γ -**Glutamyl**

transpeptidase 11062-77-4, Superoxide
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(γ -glutamyl transpeptidase
expression and superoxide production in Mpv17-/- glomerulosclerosis murine model)
IT 9013-66-5, Glutathione peroxidase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(γ -glutamyl transpeptidase,
glutathione peroxidase, and superoxide in Mpv17-/- glomerulosclerosis murine model)
IT 9054-89-1, Superoxide dismutase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(γ -glutamyl transpeptidase,
superoxide dismutase, and superoxide in Mpv17-/- glomerulosclerosis murine model)
IT 7782-44-7, Oxygen, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(γ -glutamyl transpeptidase,
superoxide production, and reactive oxygen species in Mpv17-/- glomerulosclerosis murine model)
RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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IT 9046-27-9, γ -Glutamyl transpeptidase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(γ -glutamyl transpeptidase
expression and superoxide production in Mpv17-/- glomerulosclerosis murine model)
RN 9046-27-9 HCAPLUS
CN Glutamyltransferase, γ- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

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L77 ANSWER 1 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:202498 HCAPLUS
DN 141:52221
ED Entered STN: 12 Mar 2004
TI Increased Oxidative Stress in the Mouse Adriamycin Model of Glomerulosclerosis Is Accompanied by Deposition of Ferric Iron and Altered GGT Activity in Renal Cortex
AU Ceyssens, Bart; Pauwels, Marina; Meulemans, Bart; Verbeelen, Dierik; Van den Branden, Christiane
CS Department of Human Anatomy, Vrije Universiteit Brussel and Academic Hospital of the Vrije Universiteit Brussel, Brussels, Belg.
SO Renal Failure (2004), 26(1), 21-27
CODEN: REFAE8; ISSN: 0886-022X

PB Marcel Dekker, Inc.
DT Journal
LA English
CC 14-12 (Mammalian Pathological Biochemistry)
AB Chronic renal failure evolves inevitable towards glomerular and tubulo-interstitial sclerosis. This pathol. process involves a disturbed redox status of the kidney tissue, leading to irreversible damage. In this study the authors investigate in an adriamycin model of chronic renal failure in mice the evolution of in vivo hydrogen peroxide production, and the possible role of γ -glutamyl transpeptidase and Fe3+ in the process. Histol. changes and Fe3+ deposits are evaluated by histochem. staining. To evaluate oxidative stress residual catalase activity, TBARS formation and γ -glutamyl transpeptidase activity are measured spectrophotometrically. While catalase activity remains the same, a decreased residual catalase activity indicates an increased formation of H2O2. Both the activity of γ -glutamyl transpeptidase and TBARS formation is increased at early stages of the disease. Fe3+ is clearly present in the proximal tubule. Twenty days after adriamycin injection all parameters decrease, probably due to the destruction of the tissue. These data show the involvement of oxidative stress in the progression of adriamycin induced renal failure in mice. Both radical production and oxidative damage are measurable, while the altered activity of γ -glutamyl transpeptidase and the deposition of Fe3+ suggest the involvement of these factors in the development of a disturbed redox status in the kidney cortex.
ST oxidative stress iron glutamyl transpeptidase kidney cortex glomerulosclerosis model
IT **Kidney**
(cortex; increased oxidative stress, Fe3+ deposition, and altered GGT activity in renal cortex in **glomerulosclerosis** in mouse adriamycin model)
IT **Kidney, disease**
(**failure, chronic**; increased oxidative stress, Fe3+ deposition, and altered GGT activity in renal cortex in **glomerulosclerosis** in mouse adriamycin model)
IT **Kidney, disease**
(**glomerulosclerosis**; increased oxidative stress, Fe3+ deposition, and altered GGT activity in renal cortex in **glomerulosclerosis** in mouse adriamycin model)
IT Disease models
Oxidative stress, biological
(increased oxidative stress, Fe3+ deposition, and altered GGT activity in renal cortex in glomerulosclerosis in mouse adriamycin model)
IT Peroxidation
(lipid; lipid peroxidn. in increased oxidative stress, Fe3+ deposition, and altered GGT activity in renal cortex in glomerulosclerosis in mouse adriamycin model)
IT Lipids, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(peroxidn.; lipid peroxidn. in increased oxidative stress, Fe3+ deposition, and altered GGT activity in renal cortex in glomerulosclerosis in mouse adriamycin model)
IT 7722-84-1, Hydrogen peroxide, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(H2O2 in increased oxidative stress, Fe3+ deposition, and altered GGT activity in renal cortex in glomerulosclerosis in mouse adriamycin model)
IT 9001-05-2, Catalase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(catalase in increased oxidative stress, Fe3+ deposition, and altered GGT activity in renal cortex in glomerulosclerosis in mouse adriamycin model)
IT **9046-27-9, γ -Glutamyl transpeptidase** 20074-52-6, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(increased oxidative stress, Fe3+ deposition, and altered GGT activity in renal cortex in glomerulosclerosis in mouse adriamycin model)

RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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IT **9046-27-9, γ -Glutamyl transpeptidase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(increased oxidative stress, Fe3+ deposition, and altered GGT activity in renal cortex in glomerulosclerosis in mouse adriamycin model)

RN 9046-27-9 HCAPLUS

CN Glutamyltransferase, γ- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L77 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2000:491305 HCAPLUS

DN 133:206321

ED Entered STN: 20 Jul 2000

TI Targeted expression of a dominant-negative EGF-R in the kidney reduces tubulo-interstitial lesions after renal injury

AU Terzi, Fabiola; Burtin, Martine; Hekmati, Mehrak; Federici, Pierre; Grimber, Giselle; Briand, Pascale; Friedlander, Gerard

CS Institut National de la Sante et de la Recherche Medicale (INSERM) Unite 426 and Department of Physiology, Faculte de Medecine Xavier Bichat, Universite Paris 7, Paris, 75870, Fr.

SO Journal of Clinical Investigation (2000), 106(2), 225-234
CODEN: JCINAO; ISSN: 0021-9738

PB American Society for Clinical Investigation

DT Journal

LA English

CC 14-12 (Mammalian Pathological Biochemistry)

AB The role of EGF in the evolution of renal lesions after injury is still controversial. To determine whether the EGF expression is beneficial or detrimental, we generated transgenic mice expressing a COOH-terminal-truncated EGF-R under the control of the kidney-specific type 1 γ -glutamyl transpeptidase promoter. As expected, the transgene was expressed exclusively at the basolateral membrane of proximal tubular cells. Under basal conditions, transgenic mice showed normal renal morphol. and function. Infusion of EGF to transgenic animals revealed that the mutant receptor behaved in a dominant-neg. manner and prevented EGF-signaled EGF-R autophosphorylation. We next evaluated the impact of transgene expression on the development of renal lesions in two models of renal injury. After 75% reduction of renal mass, tubular dilations were less severe in transgenic mice than in wild-type animals. After prolonged renal ischemia, tubular atrophy and interstitial fibrosis were reduced in transgenic mice as compared with wild-type mice. The beneficial effect of the transgene included a reduction of tubular cell proliferation, interstitial collagen accumulation, and mononuclear cell infiltration. In conclusion, functional inactivation of the EGF-R in renal proximal tubular cells reduced tubulo-interstitial lesions after renal injury. These data suggest that **blocking** the EGF pathway may be a therapeutic strategy to reduce the progression of chronic renal failure.

ST kidney tubulointerstitial injury EGF receptor

IT Phosphorylation, biological
(autophosphorylation; targeted expression of a dominant-neg. EGF-R in the kidney reduces tubulo-interstitial lesions after renal injury)

IT **Kidney, disease**
(**failure, chronic**; targeted expression of a dominant-neg. EGF-R in the kidney reduces tubulo-interstitial lesions after renal **injury**)

IT Kidney, disease
(interstitial fibrosis; targeted expression of a dominant-neg. EGF-R in the kidney reduces tubulo-interstitial lesions after renal injury)

IT Kidney, disease
(ischemia; targeted expression of a dominant-neg. EGF-R in the kidney reduces tubulo-interstitial lesions after renal injury)

IT Phosphorylation, biological
(receptor; targeted expression of a dominant-neg. EGF-R in the kidney reduces tubulo-interstitial lesions after renal injury)

IT Epidermal growth factor receptors
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(targeted expression of a dominant-neg. EGF-R in the kidney reduces tubulo-interstitial lesions after renal injury)

IT Kidney, disease
(tubulointerstitial; targeted expression of a dominant-neg. EGF-R in the kidney reduces tubulo-interstitial lesions after renal injury)

IT 62229-50-9, Epidermal growth factor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(targeted expression of a dominant-neg. EGF-R in the kidney reduces tubulo-interstitial lesions after renal injury)

RE.CNT 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L77 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:414925 HCAPLUS
DN 133:294841
ED Entered STN: 22 Jun 2000
TI Contribution of γ glutamyl transpeptidase to oxidative damage of ischemic rat kidney
AU Cutrin, Juan C.; Zingaro, Barbara; Camandola, Simonetta; Boveris, Alberto; Pompella, Alfonso; Poli, Giuseppe
CS Department of Clinical and Biological Sciences, University of Turin, Turin, Italy
SO Kidney International (2000), 57(2), 526-533
CODEN: KDYIA5; ISSN: 0085-2538
PB Blackwell Science, Inc.
DT Journal
LA English
CC 14-12 (Mammalian Pathological Biochemistry)
AB Background. A variety of mechanisms have been considered in the pathogenesis of the cell damage occurring in the kidney that is undergoing transient ischemia. However, little information is available about the

role of oxidative stress in building up the tissue injury in the hypoxic organ during short-term ischemia. Methods. After a standard brief period (25 min) of unilateral kidney ischemia in rats, pretreated or not with **acivicin** (60 μmol/L/kg i.v.), tissue samples from both ischemic and not ischemic kidneys were obtained to measure malondialdehyde (MDA) and glutathione (GSH) content, γ glutamyl transpeptidase (**GGT**) activity by spectrophotometry, localization and intensity of enzyme activity, and tissue damage by histochem. Results. **GGT** activity was found to be increased in both cortical and medullar zones of the ischemic kidneys, where the GSH level was only slightly decreased and the MDA level, in contrast, was markedly increased; in parallel, the cytosolic volume of the proximal tubular (PT) cells showed a significant increment. The animal pretreatment with **acivicin**, a specific **inhibitor** of **GGT**, besides preventing the up-regulation of the enzyme during ischemia, afforded good protection against the observed changes of MDA and GSH tissue levels, as well as of tubular cell volume Conclusions. Ex vivo data supporting a net pro-oxidant effect of up-regulated **GGT** during short-term ischemia of rat kidney have been obtained. The enzyme stimulation appears to contribute to the renal morphol. damage exerted by a brief hypoxic condition at the level of PT cells. The actual impact on kidney function by **GGT**-dependent oxidative damage during transient ischemia and the potential protective action of **GGT inhibitors** require subsequent investigation.

ST glutamyl transpeptidase kidney ischemia oxidative damage

IT Kidney
(cortex; γ glutamyl transpeptidase role in oxidative damage of ischemic rat kidney)

IT Cytoplasm
(cytosol; γ glutamyl transpeptidase role in oxidative damage of ischemic rat kidney)

IT **Kidney, disease**
(**ischemia**; γ glutamyl transpeptidase role in oxidative damage of ischemic rat kidney)

IT Transplant and Transplantation
Transplant and Transplantation
(kidney; γ glutamyl transpeptidase role in oxidative damage of ischemic rat kidney)

IT Peroxidation
(lipid; γ glutamyl transpeptidase role in oxidative damage of ischemic rat kidney)

IT Kidney
(medulla; γ glutamyl transpeptidase role in oxidative damage of ischemic rat kidney)

IT Lipids, biological studies
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(peroxidn.; γ glutamyl transpeptidase role in oxidative damage of ischemic rat kidney)

IT Kidney
(proximal tubule; γ glutamyl transpeptidase role in oxidative damage of ischemic rat kidney)

IT Kidney
Kidney
(transplant; γ glutamyl transpeptidase role in oxidative damage of ischemic rat kidney)

IT Oxidative stress, biological
(γ glutamyl transpeptidase role in oxidative damage of ischemic rat kidney)

IT 9046-27-9, γ Glutamyl transpeptidase
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(γ glutamyl transpeptidase role in oxidative damage of ischemic rat kidney)

IT 70-18-8, Glutathione, biological studies 542-78-9, Malondialdehyde

RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(γ glutamyl transpeptidase role in oxidative damage of ischemic rat kidney)

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L77 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:668606 HCAPLUS
DN 132:164752
ED Entered STN: 21 Oct 1999
TI Transglutaminase transcription and antigen translocation in experimental renal scarring
AU Johnson, Timothy S.; Skill, N. James; El Nahas, A. Meguid; Oldroyd, Simon D.; Thomas, Graham L.; Douthwaite, Julie A.; Haylor, John L.; Griffin, Martin
CS Northern General Hospital Trust, Sheffield Kidney Institute, Sheffield, NG11 8NS, UK
SO Journal of the American Society of Nephrology (1999), 10(10), 2146-2157
CODEN: JASNEU; ISSN: 1046-6673
PB Lippincott Williams & Wilkins
DT Journal
LA English
CC 14-12 (Mammalian Pathological Biochemistry)
AB It was recently demonstrated that renal tissue transglutaminase (tTg)

protein and its catalytic product the ε(γ-glutamyl) lysine protein cross-link are significantly increased in the subtotal (5/6) nephrectomy model (SNx) of renal fibrosis in rats. It was proposed that the enzyme had two important physiol. functions in disease development; one of stabilizing the increased extracellular matrix (ECM) by protein crosslinking, the other in a novel form of tubular cell death. This study, using the same rat SNx model, demonstrates first by Northern blotting that expression of tTg mRNA when compared with controls is increased by day 15 (+70% increase), then rises steadily, peaking at day 90 (+391%), and remains elevated at 120 d (+205%) when compared with controls. In situ hybridization histochem. demonstrated that the tubular cells were the major site of the addnl. tTg synthesis. Immunohistochem. on cryostat sections revealed a sixfold increase in ECM-bound tTg antigen at 90-d post-SNx, whereas in situ transglutaminase activity demonstrated by the incorporation of fluorescein cadaverine into cryostat sections indicated a 750% increase on day 90 in SNx animals. This increased activity was extracellular and predominantly found in the peritubular region. These results indicate that increased tTg gene transcription by tubular cells underlies the major changes in renal tTg protein reported previously in SNx rats, and that the presence of the ε(γ-glutamyl) lysine cross-links in the extracellular environment is the result of the extracellular action of tTg. These changes may be in response to tubular cell injury during the scarring process and are likely to contribute to the progressive expansion of the ECM in renal fibrosis.

ST transglutaminase transcription tubular cell extracellular activity renal scarring

IT Crosslinking
(effect of transglutaminase crosslinking on matrix metalloproteinase 1 degradation of collagen in relation to renal scarring)

IT Collagens, biological studies
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(effect of transglutaminase crosslinking on matrix metalloproteinase 1 degradation of collagen in relation to renal scarring)

IT Kidney, disease
(glomerulosclerosis; transglutaminase transcription in tubular cells and extracellular enzyme protein/activity in exptl. renal scarring)

IT Kidney, disease
(interstitial fibrosis; transglutaminase transcription in tubular cells and extracellular enzyme protein/activity in exptl. renal scarring)

IT Extracellular matrix
Transcription, genetic
(transglutaminase transcription in tubular cells and extracellular enzyme protein/activity in exptl. renal scarring)

IT mRNA
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PROC (Process)
(transglutaminase transcription in tubular cells and extracellular enzyme protein/activity in exptl. renal scarring)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(transglutaminase transcription in tubular cells and extracellular enzyme protein/activity in exptl. renal scarring)

IT Kidney
(tubule; transglutaminase transcription in tubular cells and extracellular enzyme protein/activity in exptl. renal scarring)

IT 9001-12-1, Collagenase
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effect of transglutaminase crosslinking on matrix metalloproteinase 1 degradation of collagen in relation to renal scarring)

IT 17105-15-6, ε(γ-Glutamyl) lysine
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(effect of transglutaminase crosslinking on matrix metalloproteinase 1 degradation of collagen in relation to renal scarring)

IT **80146-85-6, Glutaminylpeptide γ - glutamyltransferase**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(transglutaminase transcription in tubular cells and extracellular enzyme protein/activity in exptl. renal scarring)

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IT **80146-85-6, Glutaminylpeptide γ -**

glutamyltransferase
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(transglutaminase transcription in tubular cells and extracellular enzyme protein/activity in exptl. renal scarring)
RN 80146-85-6 HCAPLUS
CN Glutamyltransferase, glutaminylpeptide γ- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L77 ANSWER 5 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:414377 HCAPLUS
DN 131:193953
ED Entered STN: 07 Jul 1999
TI Influence of FR 167653, an inhibitor of TNF-α and IL-1, on the cardiovascular responses to chronic infusion of lipopolysaccharide in conscious rats
AU Gardiner, S. M.; Kemp, P. A.; March, J. E.; Bennett, T.
CS School of Biomedical Sciences, Queen's Medical Centre, University of Nottingham Medical School, Nottingham, NG7 2UH, UK
SO Journal of Cardiovascular Pharmacology (1999), 34(1), 64-69
CODEN: JCPCDT; ISSN: 0160-2446
PB Lippincott Williams & Wilkins
DT Journal
LA English
CC 1-8 (Pharmacology)
AB Conscious, male Long Evans rats (350-450 g) chronically instrumented for the measurement of regional hemodynamics, were infused with FR 167653, a dual **inhibitor** of tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1) synthesis (0.32 mg/kg/h) for 24 h, beginning 1 h before coinfusion of saline, or with saline for 24 h beginning 1 h before coinfusion of lipopolysaccharide (150 μg/kg/h), or with FR 167653 beginning 1 h before coinfusion of lipopolysaccharide. Animals infused with FR 167653 and saline showed progressive hindquarters vasoconstriction over the 24-h period, but this was not different from the change seen in animals (n = 3) infused with saline alone. However, plasma anal. at the end of the coinfusion of FR 167653 and saline showed substantial elevation in levels of creatine kinase, lactate dehydrogenase, and potassium, consistent with some tissue damage (heart, liver, or skeletal muscle, or a combination of these). Animals coinfused with saline and lipopolysaccharide showed biphasic decreases in mean arterial blood pressure accompanied by renal hyperemic vasodilatation, and decreases followed by increases in mesenteric and hindquarters flows and vascular conductances. At the end of the infusion period, plasma anal. showed signs of renal dysfunction (elevated creatinine) and hepatic dysfunction (elevated alkaline phosphatase, γ **-glutamyl transferase**, and alanine aminotransferase). In the presence of FR 167653, the hypotensive effects of lipopolysaccharide were abolished, but regional hemodynamics were unchanged, as were signs of organ dysfunction. One explanation of these observations is that FR 167653 causes a relative improvement in cardiac function during infusion of lipopolysaccharide, and this opposes the hypotensive effects of the latter, in spite of its persistent vasodilator effects.
ST endotoxic shock cardiovascular system FR 167653; organ damage endotoxemia FR 167653; hypotension endotoxemia FR 167653
IT Heart, disease
(cardiomyopathy; effects of FR 167653 on cardiovascular responses to chronic infusion of lipopolysaccharide in conscious rats)
IT Cardiovascular system
Hypotension
(effects of FR 167653 on cardiovascular responses to chronic infusion of lipopolysaccharide in conscious rats)
IT Interleukin 1
Tumor necrosis factors

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(effects of FR 167653 on cardiovascular responses to chronic infusion of lipopolysaccharide in conscious rats)
IT **Kidney, disease**
Liver, disease
Muscle, disease
(injury; effects of FR 167653 on cardiovascular responses to chronic infusion of lipopolysaccharide in conscious rats)
IT Vasodilation
(renal hyperemic; effects of FR 167653 on cardiovascular responses to chronic infusion of lipopolysaccharide in conscious rats)
IT Shock (circulatory collapse)
(septic; effects of FR 167653 on cardiovascular responses to chronic infusion of lipopolysaccharide in conscious rats)
IT 158876-66-5, FR 167653
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of FR 167653 on cardiovascular responses to chronic infusion of lipopolysaccharide in conscious rats)
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L77 ANSWER 6 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1997:409983 HCAPLUS
DN 127:134251
ED Entered STN: 02 Jul 1997
TI The role of transglutaminase in the rat subtotal nephrectomy model of renal fibrosis
AU Johnson, Timothy S.; Griffin, Martin; Thomas, Graham L.; Skill, James; Cox, Ann; Yang, Bin; Nicholas, Ben; Birckbichler, Paul J.; Muchaneta-Kubara, Chiwoneso; El Nahas, A. Meguid
CS Sheffield Kidney Institute, Northern General Hospital NHS Trust, Sheffield, S5 7AU, UK
SO Journal of Clinical Investigation (1997), 99(12), 2950-2960
CODEN: JCINAO; ISSN: 0021-9738
PB Rockefeller University Press
DT Journal
LA English

CC 14-12 (Mammalian Pathological Biochemistry)

AB Tissue transglutaminase is a calcium-dependent enzyme that catalyzes the crosslinking of polypeptide chains, including those of extracellular matrix (ECM) proteins, through the formation of ε-(γ-glutamyl)lysine bonds. This crosslinking leads to the formation of protein polymers that are highly resistant to degradation As a consequence, the enzyme has been implicated in the deposition of ECM protein in fibrotic diseases such as pulmonary fibrosis and atherosclerosis. In this study, the authors have investigated the involvement of tissue transglutaminase in the development of kidney fibrosis in adult male Wistar rats submitted to subtotal nephrectomy (SNx). Groups of six rats were killed on days 7, 30, 90, and 120 after SNx. As previously described, these rats developed progressive glomerulosclerosis and tubulo-interstitial fibrosis. The tissue level of ε-(γ-glutamyl)lysine cross-link (as determined by exhaustive proteolytic digestion followed by cation exchange chromatog.) increased from 3.47 in control to 13.24 nmol/g protein 90 d after SNx,. Levels of ε-(γ-glutamyl)lysine cross-link correlated well with the renal fibrosis score throughout the 120 observation days (r = 0.78). Tissue homogenates showed no significant change in overall transglutaminase activity (14C putrescine incorporation assay) unless adjusted for the loss of viable tubule cells, when an increase from 5.77 to 13.93 U/mg DNA in cytosolic tissue transglutaminase activity was seen. This increase was supported by Western blot anal., showing a parallel increase in renal tissue transglutaminase content. Immunohistochem. demonstrated that this large increase in ε-(γ-glutamyl)lysine cross-link and tissue transglutaminase took place predominantly in the cytoplasm of tubular cells, while immunofluorescence also showed low levels of the ε-(γ-glutamyl)lysine cross-link in the extracellular renal interstitial space. The number of cells showing increases in tissue transglutaminase and its cross-link product, ε-(γ-glutamyl)lysine, appeared greater than those showing signs of typical apoptosis as determined by in situ end-labeling. This observed association between tissue transglutaminase, ε-(γ-glutamyl)lysine cross-link, and renal tubulointerstitial scarring in rats submitted to SNx suggests that tissue transglutaminase may play an important role in the development of exptl. renal fibrosis and the associated loss of tubule integrity.

ST transglutaminase subtotal nephrectomy model renal fibrosis

IT **Kidney, disease**
(**glomerulosclerosis**; renal transglutaminase and ε-(γ-glutamyl)lysine in rat subtotal nephrectomy model of renal **fibrosis**)

IT Kidney, disease
(interstitial fibrosis; renal transglutaminase and ε-(γ-glutamyl)lysine in rat subtotal nephrectomy model of renal fibrosis)

IT Cytoplasm
Disease models
Extracellular matrix
(renal transglutaminase and ε-(γ-glutamyl)lysine in rat subtotal nephrectomy model of renal fibrosis)

IT **80146-85-6, Glutaminylpeptide γ - glutamyltransferase**
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(renal transglutaminase and ε-(γ-glutamyl)lysine in rat subtotal nephrectomy model of renal fibrosis)

IT 17105-15-6, ε-(γ-Glutamyl)lysine
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(renal transglutaminase and ε-(γ-glutamyl)lysine in rat subtotal nephrectomy model of renal fibrosis)

IT **80146-85-6, Glutaminylpeptide γ - glutamyltransferase**
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological

study); OCCU (Occurrence)
(renal transglutaminase and ε-(γ-glutamyl)lysine in rat subtotal nephrectomy model of renal fibrosis)
RN 80146-85-6 HCAPLUS
CN Glutamyltransferase, glutaminylpeptide γ- (9CI) (CA INDEX NAME)

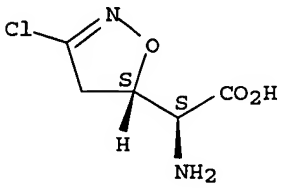
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L77 ANSWER 7 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1988:53265 HCAPLUS
DN 108:53265
ED Entered STN: 20 Feb 1988
TI Effects of **inhibition** and modulation of **gamma-glutamyltransferase** on **glutamine** and glutamate metabolism in control and acidotic rat proximal tubules
AU Dass, Proveen D.; Lawson, Lydia R.; Delaney, Vera; Bourke, Edmund
CS Sch. Med., Emory Univ., Atlanta, GA, USA
SO Mineral and Electrolyte Metabolism (1987), 13(6), 433-41
CODEN: MELMDI; ISSN: 0378-0392
DT Journal
LA English
CC 13-2 (Mammalian Biochemistry)
AB In rat proximal tubules, compds. known to activate γ-**glutamyltransferase** (γ -**GT**) including the endogenously produced organic anion hippurate, induced a significant increase in glutamine-ammoniagenesis both in nonacidosis and chronic metabolic acidosis, although in absolute terms the increase was not more marked under the latter conditions. AT-125, which irreversibly inactivates . **gamma.-GT**, but not phosphate-dependent glutaminase, reduced the production of NH3 from glutamine in both acid-base states. In absolute terms, again, this reduction was similar under both acid-base conditions, implying an unimportant role for γ -**GT** in vitro in the augmentation in renal ammoniagenesis induced by chronic metabolic acidosis. Maleate-stimulated glutamine-ammoniagenesis, recently attributed to its intramitochondrial **inhibitory** effect in the dog, is substantially due to the activation of γ -**GT** in rat proximal tubules.
ST **glutamyltransferase** gamma kidney regulation; glutamine ammonia metab kidney
IT Gluconeogenesis
(from glutamine, maleate and other compds. inhibition of, in kidney proximal tubule)
IT **Acidosis**
(chronic, γ- **glutamyltransferase** regulation in kidney proximal tubule in relation to)
IT Kidney, metabolism
(proximal tubule, glutamate and glutamine metabolism by, γ-**glutamyltransferase** regulation in, acidosis in relation to)
IT 7664-41-7, Ammonia, biological studies
RL: FORM (Formation, nonpreparative)
(formation of, from glutamine, regulation of, γ-**glutamyltransferase** regulation in kidney proximal tubule in)
IT 65-85-0, Benzoic acid, biological studies
RL: BIOL (Biological study)
(glutamate and glutamine metabolism by kidney proximal tubule response to, γ- **glutamyltransferase** in)
IT 56-86-0, Glutamic acid, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metabolism of, by kidney proximal tubule, γ-**glutamyltransferase** regulation in)
IT 56-85-9, Glutamine, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metabolism of, in kidney proximal tubule, γ-**glutamyltransferase** regulation in)

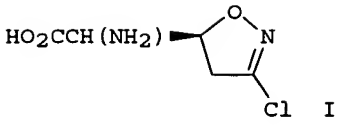
IT 9046-27-9, γ- Glutamyltransferase
RL: PROC (Process)
(of kidney proximal tubule, regulation of, in glutamate and glutamine metabolism regulation, acidosis in relation to)
IT 151-21-3, biological studies
RL: BIOL (Biological study)
(γ- glutamyltransferase inactivation by AT-125 in presence of, in kidney proximal tubule, glutamate and glutamine metabolism in response to)
IT 42228-92-2, AT-125
RL: BIOL (Biological study)
(γ- glutamyltransferase inactivation by, in kidney proximal tubule, glutamate and glutamine metabolism in response to)
IT 61-78-9, p-Aminohippuric acid 110-16-7, Maleic acid, biological studies
495-69-2, Hippuric acid 2051-95-8, 3-Benzoylpropionic acid
RL: BIOL (Biological study)
(γ- glutamyltransferase stimulation by, in kidney proximal tubule, glutamate and glutamine metabolism response to)
IT 9046-27-9, γ- Glutamyltransferase
RL: PROC (Process)
(of kidney proximal tubule, regulation of, in glutamate and glutamine metabolism regulation, acidosis in relation to)
RN 9046-27-9 HCAPLUS
CN Glutamyltransferase, γ- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT 42228-92-2, AT-125
RL: BIOL (Biological study)
(γ- glutamyltransferase inactivation by, in kidney proximal tubule, glutamate and glutamine metabolism in response to)
RN 42228-92-2 HCAPLUS
CN 5-Isoxazoleacetic acid, α-amino-3-chloro-4,5-dihydro-, (αS,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L77 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1987:470402 HCAPLUS
DN 107:70402
ED Entered STN: 05 Sep 1987
TI Embryotoxicity elicited by inhibition of γ-glutamyltransferase by Acivicin and transferase antibodies in cultured rat embryos
AU Stark, Kevin L.; Harris, Craig; Juchau, Mont R.
CS Sch. Med., Univ. Washington, Seattle, WA, 98195, USA
SO Toxicology and Applied Pharmacology (1987), 89(1), 88-96
CODEN: TXAPA9; ISSN: 0041-008X
DT Journal
LA English
CC 1-6 (Pharmacology)
GI



I

AB **Acivicin** (AT-25; I) and IgG isolated from goat anti-γ-**glutamyltransferase** antiserum were used to **inhibit** the activity of γ -**glutamyl transferase** (**GGT**, **EC 2.3.2.2**) in rat conceptuses cultured from days 10 to 11 of gestation. **Inhibition** of **GGT** by either **Acivicin** or anti-**GGT** IgG produced embryotoxicity and malformations, although each compound produced a unique spectrum of effects. **Acivicin**, at an initial concentration in the culture medium of 5 μM, produced a marked decrease in yolk sac vasculature and was associated with embryonic malformations such as neural tube necrosis, microophthalmia, and cephalic edema after 24 h exposure. These malformations were accompanied by significant decreases in both embryonic and yolk sac protein, yolk sac **GGT** activity, as well as embryonic GSH levels. In contrast, anti-**GGT** IgG produced no apparent effects on yolk sac vasculature or protein after exposure of conceptuses to an initial concentration of 50 μg IgG/mL culture medium, even though equal **inhibition** of yolk sac **GGT** (30%) was achieved by each **inhibitor.** Exposure to IgG (50 μg/mL) for 24 h was associated with decreased embryonic protein; decreased levels of GSH in the embryo were observed after both 3 and 24 h. The dichotomy of effects on the yolk sac by the 2 compds. indicates that **Acivicin** produced these effects by mechanisms other than by **GGT inhibition** alone. Evidently the **inhibition** of **GGT** in rat embryos undergoing organogenesis can elicit embryotoxic effects and produce alterations in GSH levels. The capacity of the anti-**GGT** antibody to **inhibit** the **GGT** activity in the yolk sac (while having no apparent effect on yolk sac morphol.), and yet influence the embryo by decreasing protein and GSH levels, underscores the important role of the yolk sac during the highly sensitive stages of organogenesis.

ST **glutamyltransferase Acivicin** embryo; teratogenesis
Acivicin glutamyltransferase

IT **Teratogenesis**
(**Acivicin** and **glutamyltransferase** antibodies in relation to)

IT Antibodies
RL: **BIOL (Biological study)**
(to **glutamyltransferase**, embryonic growth parameters response to, **Acivicin** embryo toxicity in relation to)

IT **42228-92-2, Acivicin**
RL: **BIOL (Biological study)**
(embryo toxicity of, **glutamyltransferase inhibition** in relation to)

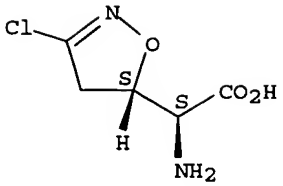
IT 70-18-8, Glutathione, biological studies
RL: **BIOL (Biological study)**
(of embryo, **Acivicin** effect on)

IT **42228-92-2, Acivicin**
RL: **BIOL (Biological study)**
(embryo toxicity of, **glutamyltransferase inhibition** in relation to)

RN 42228-92-2 HCAPLUS

CN 5-Isoxazoleacetic acid, α-amino-3-chloro-4,5-dihydro-, (αS,5S)- (9CI) (CA INDEX NAME)

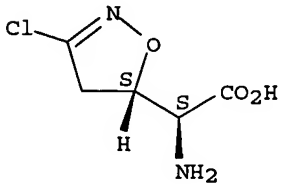
Absolute stereochemistry.



L77 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1982:16560 HCAPLUS
DN 96:16560
ED Entered STN: 12 May 1984
TI Differential effect of AT-125 on rat renal glutaminase activities
AU Shapiro, Richard A.; Curthoys, Norman P.
CS Sch. Med., Univ. Pittsburgh, Pittsburgh, PA, 15261, USA
SO FEBS Letters (1981), 133(1), 131-4
CODEN: FEBLAL; ISSN: 0014-5793
DT Journal
LA English
CC 7-3 (Enzymes)
Section cross-reference(s): 13, 14
AB AT-125, a glutamine **antagonist**, **inhibits** the γ-**glutamyltranspeptidase** (I) and the associated phosphate-independent glutaminase (II) activity of rat kidney brush border membranes without affecting the phosphate-dependent II. This selective **inhibition** of phosphate-independent II activity by AT-125 enables the determination of the relative contribution of the II activities to glutamine metabolism in crude homogenates and further substantiates that the **inhibited** activity is due to I, as both glutamine and γ-glutamyl-p-nitroanilide substrate utilization is **inhibited**. Injection of AT-125 **inhibited** I activity in vivo but had only a slight effect (.apprx.1,3-fold increase) on NH3 excretion in rats made acutely acidotic and no effect on increased plasma glutamine or urine acidification associated with acute acidosis. Thus, I is not essential to the adaptive increase in NH3 synthesis observed with the onset of acidosis.
ST glutaminase **inhibition** **AT125**
glutamyltranspeptidase kidney; acidosis
glutamyltranspeptidase glutaminase kidney
IT Kidney, composition
(glutamyl transpeptidase and associated glutaminase activity of brush border membrane of, AT-125 selective inhibition of)
IT **Acidosis**
(**glutamyltranspeptidase** of kidney brush border membrane in relation to)
IT **42228-92-2**
RL: **BIOL** (Biological study)
(glutaminase activity of **glutamyltranspeptidase** **inhibition** by, selective glutaminase determination in relation to)
IT **9046-27-9**
RL: BIOL (Biological study)
(glutaminase activity of, of kidney brush border membrane, ATP-125 selective **inhibition** of)
IT 9001-47-2
RL: BIOL (Biological study)
(**glutamyltranspeptidase**-associated, of kidney brush border membrane, AT-125 selective **inhibition** of)
IT 9001-78-9
RL: BIOL (Biological study)
(of kidney brush border membrane, in acidosis)
IT 14798-03-9, biological studies
RL: BIOL (Biological study)
(resorption of, by kidney in acidosis, **glutamyltranspeptidase** in relation to)

IT 42228-92-2
RL: BIOL (Biological study)
(glutaminase activity of **glutamyltranspeptidase inhibition** by, selective glutaminase determination in relation to)
RN 42228-92-2 HCAPLUS
CN 5-Isoxazoleacetic acid, α-amino-3-chloro-4,5-dihydro-, (αS,5S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 9046-27-9
RL: BIOL (Biological study)
(glutaminase activity of, of kidney brush border membrane, ATP-125 selective **inhibition** of)
RN 9046-27-9 HCAPLUS
CN Glutamyltransferase, γ- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> b home
FILE 'HOME' ENTERED AT 15:50:49 ON 21 JUN 2005

=>

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=> d his full

     (FILE 'HOME' ENTERED AT 07:58:31 ON 22 JUN 2005)

     FILE 'REGISTRY' ENTERED AT 07:58:48 ON 22 JUN 2005
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                  WO2002-EP1799#)/AP,PRN
L2                SEL PLU=ON  L1 1- RN :      35 TERMS
L3   (         35)SEA ABB=ON  PLU=ON  L2
L4   (          2)SEA ABB=ON  PLU=ON  L3 AND GAMMA
L5              1 SEA ABB=ON  PLU=ON  L4 AND ?TRANSFER?/CNS
                ---------
                ACT HAR325INHB/A
                ---------
L6            494 SEA ABB=ON  PLU=ON  (GAMMA (1A)(GT# OR GLUTAMYLPEPTIDAS? OR
                  GLUTAMYLTRANSFERAS? OR GLUTAMYL (1A) (?PEPTIDAS? OR ?TRANSFERAS
                  E?)))/CNS
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                ACT HAR325C10/A
                ---------
L7   (         11)SEA ABB=ON  PLU=ON  C5H7CLN2O3 AND NOC3/ES
L8              9 SEA ABB=ON  PLU=ON  L7 NOT (ACETAMIDE OR COMPD OR COMPOUND)
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                ACT HAR325F0/A
                ---------
L9                STR
L10           119 SEA SSS FUL L9
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     FILE 'HCAPLUS' ENTERED AT 08:00:40 ON 22 JUN 2005
                ACT HAR325ACI/Q
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L11               QUE ABB=ON  PLU=ON  ISOXZOLACET?(1A) ACID (1A)AMINO(1A)CHLORO
                  (2A)(DIHYDRO OR DI (1A)HYDRO) OR ACIVICIN# OR AT125 OR
                  AT(1A)125 OR NSC163501 OR NSC(1A)(163501 OR 163(1A)501) OR
                  U42126 OR U(1A)(42126 OR 42(1A)126)
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                ACT HAR325GGT/Q
                ---------
L12               QUE ABB=ON  PLU=ON  GLUTAMYLTRANSFERAS? OR GLUTAMYLPEPTIDAS?
                  OR GLUTAMYLTRANSPEPTIDAS? OR GGT OR GAMMA (1A) (GT# OR GPT OR
                  GLUTAM? (1A)(?PEPTIDAS? OR ?TRANSFERAS?)) OR "EC2.3.2.2" OR
                  "E.C.2.3.2.2" OR (EC OR E(1A)C) (1A)"2.3.2.2"

     FILE 'MEDLINE' ENTERED AT 08:39:18 ON 22 JUN 2005
L13         18645 SEA ABB=ON  PLU=ON  L5 OR L6 OR L12
L15               QUE ABB=ON  PLU=ON  (C12.777.419. OR GLOMERULONEPHRITIS,
                  MEMBRANOUS+NT OR DIABETIC NEUROPATHIES+NT)/CT
L16            25 SEA ABB=ON  PLU=ON  L14 AND L15
L17            20 SEA ABB=ON  PLU=ON  L16 AND PY<=2001
                  D TRI TOT
L18             8 SEA ABB=ON  PLU=ON  (L8 OR L10 OR L11) AND L17
                  D TRI TOT
                  E WEIHER H/AU
L19            35 SEA ABB=ON  PLU=ON  ("WEIHER H"/AU OR "WEIHER HANS"/AU)
                  E SIES H/AU
L20           475 SEA ABB=ON  PLU=ON  ("SIES H"/AU OR "SIES HELMUT"/AU)
                  E WAGNER G/AU
L21          1800 SEA ABB=ON  PLU=ON  ("WAGNER G"/AU OR "WAGNER G A"/AU OR
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                  "WAGNER G G"/AU OR "WAGNER G GALE"/AU OR "WAGNER G H"/AU OR
                  "WAGNER G J"/AU OR "WAGNER G L"/AU OR "WAGNER G LOUIS"/AU OR
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                  "WAGNER G R"/AU OR "WAGNER G S"/AU OR "WAGNER G W"/AU)
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                E WAGNER GUNT/AU
L22          26 SEA ABB=ON  PLU=ON  ("WAGNER GUNTER P"/AU OR "WAGNER GUNTHER
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L24           0 SEA ABB=ON  PLU=ON  L18 AND (L19 OR L20 OR L21 OR L22 OR L23)
                SEL AN L18 1-2 5-8
L25           6 SEA ABB=ON  PLU=ON  (1998110948/AN OR 2000117960/AN OR
                88322348/AN OR 90176799/AN OR 91335465/AN OR 91376832/AN) AND
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L26         343 SEA ABB=ON  PLU=ON  L14 AND (C1. OR C2. OR C3. OR C4. OR C5.
                OR C6. OR C7. OR C8. OR C9. OR C10. OR C11. OR C12. OR C13. OR
                C14. OR C15. OR C16. OR C17. OR C18. OR C19. OR C20. OR C21.
                OR C22. OR C23.)/CT
L27          42 SEA ABB=ON  PLU=ON  L26 AND (L8 OR L10 OR L11)
L28          35 SEA ABB=ON  PLU=ON  L27 AND PY<=2001
L29          27 SEA ABB=ON  PLU=ON  L28 NOT L18
L30          16 SEA ABB=ON  PLU=ON  (2001146599/AN OR 2002023208/AN OR
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                95042327/AN OR 96063893/AN OR 96231934/AN OR 96303179/AN OR
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                (2A)(DIHYDRO OR DI (1A)HYDRO) OR ACIVICIN# OR AT125 OR
                AT(1A)125 OR NSC163501 OR NSC(1A)(163501 OR 163(1A)501) OR
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L36          31 SEA ABB=ON  PLU=ON  "WEIHER H"/AU
                E SIES H/AU
L37         413 SEA ABB=ON  PLU=ON  ("SIES H"/AU OR "SIES H M"/AU)
                E WAGNER G/AU
L38        1487 SEA ABB=ON  PLU=ON  ("WAGNER G"/AU OR "WAGNER G A"/AU OR
                "WAGNER G A L"/AU OR "WAGNER G C"/AU OR "WAGNER G E"/AU OR
                "WAGNER G F"/AU OR "WAGNER G G"/AU OR "WAGNER G H"/AU OR
                "WAGNER G J"/AU OR "WAGNER G K"/AU OR "WAGNER G L"/AU OR
                "WAGNER G M"/AU OR "WAGNER G N"/AU OR "WAGNER G P"/AU OR
                "WAGNER G R"/AU OR "WAGNER G S"/AU OR "WAGNER G W"/AU)
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L41          53 SEA ABB=ON  PLU=ON  L35 NOT L40
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                OR 88210892/AN OR 90040167/AN OR 90100113/AN OR 90116335/AN OR
                91267891/AN OR 93009711/AN OR 94362282/AN OR 96356214/AN) AND
                L41
L43          13 SEA ABB=ON  PLU=ON  (1999027532/AN OR 1999298306/AN OR
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                OR 90040167/AN OR 90100113/AN OR 90116335/AN OR 91267891/AN OR
                93009711/AN OR 94362282/AN OR 96356214/AN) AND L42

=> b medl
FILE 'MEDLINE' ENTERED AT 10:44:49 ON 22 JUN 2005

 FILE LAST UPDATED: 21 JUN 2005 (20050621/UP).  FILE COVERS 1950 TO DATE.

 On December 19, 2004, the 2005 MeSH terms were loaded.

 The MEDLINE reload for 2005 is now available.  For details enter HELP
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RLOAD at an arrow promt (=>). See also:

http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all l25 tot

L25 ANSWER 1 OF 6 MEDLINE on STN
AN 2000117960 MEDLINE
DN PubMed ID: 10652029
TI Contribution of **gamma glutamyl transpeptidase** to oxidative damage of ischemic rat kidney.
AU Cutrin J C; Zingaro B; Camandola S; Boveris A; Pompella A; Poli G
CS Department of Clinical and Biological Sciences, University of Turin, and A.Fa.R.-Fatebenefratelli Hospital, Turin, Italy. juan.cutrin@sluigi.unito.it.
SO Kidney international, **(2000 Feb)** 57 (2) 526-33.
Journal code: 0323470. ISSN: 0085-2538.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200003
ED Entered STN: 20000320
Last Updated on STN: 20000320
Entered Medline: 20000309
AB BACKGROUND: A variety of mechanisms have been considered in the pathogenesis of the cell damage occurring in the kidney that is undergoing transient ischemia. However, little information is available about the role of oxidative stress in building up the tissue injury in the hypoxic organ during short-term ischemia. METHODS: After a standard brief period (25 min) of unilateral kidney ischemia in rats, pretreated or not with **acivicin** (60 micromol/L/kg i.v.), tissue samples from both ischemic and not ischemic kidneys were obtained to measure malondialdehyde (MDA) and glutathione (GSH) content, **gamma glutamyl transpeptidase** (**GGT**) activity by spectrophotometry, localization and intensity of enzyme activity, and tissue damage by histochemistry. RESULTS: **GGT** activity was found to be increased in both cortical and medullar zones of the ischemic kidneys, where the GSH level was only slightly decreased and the MDA level, in contrast, was markedly increased; in parallel, the cytosolic volume of the proximal tubular (PT) cells showed a significant increment. The animal pretreatment with **acivicin**, a specific inhibitor of **GGT** , besides preventing the up-regulation of the enzyme during ischemia, afforded good protection against the observed changes of MDA and GSH tissue levels, as well as of tubular cell volume. CONCLUSIONS: Ex vivo data supporting a net pro-oxidant effect of up-regulated **GGT** during short-term ischemia of rat kidney have been obtained. The enzyme stimulation appears to contribute to the renal morphological damage exerted by a brief hypoxic condition at the level of PT cells. The actual impact on kidney function by **GGT**-dependent oxidative damage during transient ischemia and the potential protective action of **GGT** inhibitors require subsequent investigation.
CT Check Tags: Male
Animals
Cell Size
Cytosol: ME, metabolism
Enzyme Activation: PH, physiology

Enzyme Inhibitors: PD, pharmacology
*Ischemia: ME, metabolism
Isoxazoles: PD, pharmacology
***Kidney Diseases: EN, enzymology**
Kidney Diseases: ET, etiology
Kidney Diseases: PA, pathology
Kidney Tubules: BS, blood supply
*Kidney Tubules: EN, enzymology
Kidney Tubules: PA, pathology
Lipid Peroxidation: PH, physiology
Microsomes: EN, enzymology
*Oxidative Stress: PH, physiology
Rats
Rats, Wistar
Renal Circulation
Research Support, Non-U.S. Gov't
gamma-Glutamyltransferase: AI, antagonists & inhibitors
***gamma-Glutamyltransferase: ME, metabolism**
RN **52583-41-2 (acivicin)**
CN 0 (Enzyme Inhibitors); 0 (Isoxazoles); **EC 2.3.2.2** (**gamma-Glutamyltransferase**)

L25 ANSWER 2 OF 6 MEDLINE on STN
AN **1998110948** MEDLINE
DN PubMed ID: 9450487
TI Cytotoxicity and cell-proliferation induced by the nephrocarcinogen hydroquinone and its nephrotoxic metabolite 2,3,5-(tris-glutathion-S-yl)hydroquinone.
AU Peters M M; Jones T W; Monks T J; Lau S S
CS Division of Pharmacology and Toxicology, College of Pharmacy, University of Texas at Austin, 78712, USA.
NC ES 07784 (NIEHS)
GM 39338 (NIGMS)
SO Carcinogenesis, **(1997 Dec)** 18 (12) 2393-401.
Journal code: 8008055. ISSN: 0143-3334.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199802
ED Entered STN: 19980224
Last Updated on STN: 19980224
Entered Medline: 19980211
AB Hydroquinone, an intermediate used in the chemical industry and a metabolite of benzene, is a nephrocarcinogen in the 2-year National Toxicology Program bioassay in male Fischer 344 rats. Current evidence suggests that certain chemicals may induce carcinogenesis by a mechanism involving cytotoxicity, followed by sustained regenerative hyperplasia and ultimately tumor formation. Glutathione (GSH) conjugates of a variety of hydroquinones are potent nephrotoxicants, and we now report on the effect of hydroquinone and 2,3,5-(tris-glutathion-S-yl)hydroquinone, on site-selective cytotoxicity and cell proliferation in rat kidney. Male Fischer 344 rats (160-200 g) were treated with hydroquinone (1.8 mmol/kg or 4.5 mmol/kg, p.o.) or 2,3,5-(tris-glutathion-S-yl)hydroquinone (7.5 micromol/kg; 1.2-1.5 micromol/rat, i.v.), and blood urea nitrogen (BUN), urinary **gamma-glutamyl transpeptidase** (**gamma-GT**), alkaline phosphatase (ALP), glutathione-S-transferase (GST) and glucose were measured as indices of nephrotoxicity. Hydroquinone (1.8 mmol/kg, p.o.) is nephrotoxic in some rats, but not others, but cell proliferation (BrDU incorporation) in proximal tubular cells of the S3M region correlates with the degree of toxicity in individual rats. At 4.5 mmol/kg, hydroquinone causes significant increases in the urinary excretion of **gamma-GT**, ALP and GST. Pretreatment of rats with **acivicin** prevents hydroquinone-mediated nephrotoxicity, indicating that toxicity is dependent on the formation of metabolites that require processing by

gamma-GT. Consistent with this view, 2,3,5-(tris-glutathion-S-yl)hydroquinone, a metabolite of hydroquinone, causes increases in BUN, urinary gamma-GT and ALP, all of which are maximal 12 h after administration of 2,3,5-(tris-glutathion-S-yl)hydroquinone. In contrast, the maximal excretion of GST and glucose occurs after 24 h. By 72 h, BUN and glucose concentrations return to control levels, while gamma-GT, ALP and GST remain slightly elevated. Examination of kidney slices by light microscopy revealed the presence of tubular necrosis in the S3M segment of the proximal tubule, extending into the medullary rays. Cell proliferation rates in this region were 2.4, 6.9, 15.3 and 14.3% after 12, 24, 48 and 72 h, respectively, compared to 0.8-2.4% in vehicle controls. Together with the metabolic data, the results indicate a role for hydroquinone-thioether metabolites in hydroquinone toxicity and carcinogenicity.

CT Check Tags: Male
Animals
*Carcinogens: TO, toxicity
Cell Division: DE, drug effects
*Cell Survival: DE, drug effects
*Glutathione: AA, analogs & derivatives
Glutathione: TO, toxicity
*Hydroquinones: TO, toxicity
Isoxazoles: PD, pharmacology
*Kidney: DE, drug effects
Kidney: PA, pathology
Kidney Diseases: CI, chemically induced
Kidney Diseases: PA, pathology
Kidney Neoplasms: CI, chemically induced
Kidney Neoplasms: PA, pathology
Rats
Rats, Inbred F344
Research Support, U.S. Gov't, P.H.S.
gamma-Glutamyltransferase: AI, antagonists & inhibitors

RN 119212-33-8 (2,3,5-(triglutathion-S-yl)hydroquinone); 123-31-9 (hydroquinone); **52583-41-2 (acivicin)**; 70-18-8 (Glutathione)

CN 0 (Carcinogens); 0 (Hydroquinones); 0 (Isoxazoles); **EC 2.3.2.2** (gamma-**Glutamyltransferase**)

L25 ANSWER 3 OF 6 MEDLINE on STN

AN **91376832** MEDLINE

DN PubMed ID: 1680251

TI N-(3,5-dichlorophenyl)succinimide nephrotoxicity: evidence against the formation of nephrotoxic glutathione or cysteine conjugates.

AU Rankin G O; Shih H C; Teets V J; Yang D J; Nicoll D W; Brown P I

CS Department of Pharmacology, Marshall University School of Medicine, Huntington, WV 25755-9310.

NC DK 31210 (NIDDK)

SO Toxicology, **(1991)** 68 (3) 307-25.
Journal code: 0361055. ISSN: 0300-483X.

CY Netherlands

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199110

ED Entered STN: 19911108
Last Updated on STN: 20000303
Entered Medline: 19911023

AB The agricultural fungicide N-(3,5-dichlorophenyl)succinimide (NDPS) induces nephrotoxicity via one or more metabolites. Previous studies suggested that glutathione is important for mediating NDPS-induced nephropathy. The purpose of this study was to examine the possibility that a glutathione or cysteine conjugate of NDPS or an NDPS metabolite might be the penultimate or ultimate nephrotoxic species. In one set of experiments, male Fischer 344 rats were administered intraperitoneally (i.p.) NDPS (0.4 or 1.0 mmol/kg) 1 h after pretreatment with the gamma **glutamyltranspeptidase** inhibitor **AT-125** (

acivicin) (10 mg/kg, i.p.) and renal function was monitored at 24 and 48 h. In general, AT-125 pretreatment had few effects on NDPS-induced nephropathy. In a second set of experiments, rats were treated i.p. or orally (p.o.) with a putative glutathione (S-(2-(N-(3,5-dichlorophenyl)succinimidyl)glutathione (NDPSG), a cysteine (S-(2-(N-(3,5-dichlorophenyl)succinimidyl)cysteine (NDPSC) (as the methyl ester) or N-acetylcysteine (S-(2-(N-(3,5-dichlorophenyl)succinimidyl)-N-acetylcysteine (NDPSN) conjugate of NDPS (0.2, 0.4 or 1.0 mmol/kg) or vehicle and renal function was monitored at 24 and 48 h. An intramolecular cyclization product of NDPSC, 5-carbomethoxy-2-(N-(3,5-dichlorophenyl)carbamoylmethyl)-1,4-th iazane-3-one (NDCTO) was also examined for nephrotoxic potential. None of the compounds produced toxicologically important changes in renal function or morphology. The in vitro ability of the conjugates to alter organic ion accumulation by cortical slices was also examined. All of the conjugates tested caused a reduction in p-aminohippurate (PAH) accumulation at a conjugate bath concentration of 10(-4) M, but none of the conjugates reduced tetraethylammonium (TEA) uptake. In a third experiment, the ability of the cysteine conjugate beta-lyase inhibitor aminooxyacetic acid (AOAA) (0.5 mmol/kg, i.p.) to alter the nephrotoxicity induced by two NDPS metabolites, N-(3,5-dichlorophenyl)-2-hydroxysuccinimide (NDHS) or N-(3,5-dichlorophenyl)-2-hydroxysuccinamic acid (NDHSA) (0.2 mmol/kg, i.p.), was examined. AOAA pretreatment had no effect on NDHS- or NDHSA-induced nephrotoxicity. These results do not support a role for a glutathione or cysteine conjugate of NDPS or and NDPS metabolite as being the penultimate or ultimate nephrotoxic species.

CT Check Tags: In Vitro; Male
Aminooxyacetic Acid: PD, pharmacology
Animals
Biotransformation
*Cysteine: ME, metabolism
Fungicides, Industrial: ME, metabolism
*Fungicides, Industrial: TO, toxicity
*Glutathione: ME, metabolism
Isoxazoles: PD, pharmacology
***Kidney Diseases: CI, chemically induced**
Rats
Rats, Inbred F344
Research Support, U.S. Gov't, P.H.S.
*Succinimides: ME, metabolism
*Succinimides: TO, toxicity
gamma-Glutamyltransferase: AI, antagonists & inhibitors

RN 24096-53-5 (N-(3,5-dichlorophenyl)succinimide); 52-90-4 (Cysteine); **52583-41-2 (acivicin)**; 645-88-5 (Aminooxyacetic Acid); 70-18-8 (Glutathione)

CN 0 (Fungicides, Industrial); 0 (Isoxazoles); 0 (Succinimides); **EC 2.3.2.2 (gamma-Glutamyltransferase)**

L25 ANSWER 4 OF 6 MEDLINE on STN

AN **91335465** MEDLINE

DN PubMed ID: 1678558

TI Inhibition of **gamma-glutamyl transpeptidase** potentiates the nephrotoxicity of glutathione-conjugated chlorohydroquinones.

AU Mertens J J; Temmink J H; van Bladeren P J; Jones T W; Lo H H; Lau S S; Monks T J

CS Department of Toxicology, Agricultural University Wageningen, The Netherlands.

NC ES 04662 (NIEHS)
GM 39338 (NIGMS)

SO Toxicology and applied pharmacology, **(1991 Aug)** 110 (1) 45-60.
Journal code: 0416575. ISSN: 0041-008X.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals
EM 199109
ED Entered STN: 19911006
Last Updated on STN: 19950206
Entered Medline: 19910918
AB Administration of either 2,5-dichloro-3-(glutathion-S-yl)-1, 4-benzoquinone (DC-[GSyl]BQ) or 2,5,6-trichloro-3-(glutathion-S-yl)-1,4-benzoquinone (TC-[GSyl]BQ) to male Sprague-Dawley rats caused dose-dependent (50-200 mumol/kg; iv) renal proximal tubular necrosis, as evidenced by elevations in blood urea nitrogen (BUN), and in the urinary excretion of lactate dehydrogenase (LDH), **gamma-glutamyl transpeptidase** (**gamma-GT**) and glucose. Renal proximal tubular necrosis was also confirmed by histological examination of kidney slices prepared from DC-(GSyl)BQ- and TC-(GSyl)BQ-treated animals. Administration of the corresponding hydroquinone conjugates (DC-[GSyl]HQ and TC-[GSyl]HQ), prepared by reducing the quinones with a threefold molar excess of ascorbic acid, resulted in a substantial increase in nephrotoxicity. Moreover, in contrast to other glutathione (GSH)-conjugated hydroquinones, the nephrotoxicity of both DC-(GSyl)HQ and TC-(GSyl)HQ was potentiated when rats were pretreated with **AT-125**, an irreversible inhibitor of **gamma-GT**. Neither the quinone-GSH nor the hydroquinone-GSH conjugates caused any effect on liver histology or serum glutamate-pyruvate transaminase levels. The results suggest that coadministration of ascorbic acid with DC-(GSyl)BQ or TC-(GSyl)BQ decreases their interactions with extrarenal nucleophiles, including plasma proteins, and thus increases the concentration of the conjugates delivered to the kidney, and hence toxicity. Furthermore the ability of **AT-125** to potentiate the nephrotoxicity of DC-(GSyl)HQ and TC-(GSyl)HQ suggests that metabolism of these conjugates by **gamma-GT** constitutes a detoxication reaction.
CT Check Tags: Male
Animals
Ascorbic Acid: PD, pharmacology
*Chloranil: AA, analogs & derivatives
Chloranil: TO, toxicity
Chromatography, High Pressure Liquid
Dose-Response Relationship, Drug
Drug Synergism
Electrochemistry
*Glutathione: AA, analogs & derivatives
Glutathione: TO, toxicity
Isoxazoles: PD, pharmacology
Kidney Cortex: DE, drug effects
Kidney Cortex: PA, pathology
***Kidney Diseases: CI, chemically induced**
Kidney Diseases: PA, pathology
Kidney Tubular Necrosis, Acute: CI, chemically induced
Oxidation-Reduction
Rats
Rats, Inbred Strains
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
***gamma-Glutamyltransferase: AI, antagonists & inhibitors**
RN 117383-28-5 (2-gluthionyl-3,5,6-trichloro-1,4-benzoquinone); 118-75-2 (Chloranil); 135608-87-6 (2,5-dichloro-3-(glutathionyl-S-yl)-1,4-benzoquinone); 50-81-7 (Ascorbic Acid); **52583-41-2 (acivicin)**; 70-18-8 (Glutathione)
CN 0 (Isoxazoles); **EC 2.3.2.2** (**gamma-Glutamyltransferase**)

L25 ANSWER 5 OF 6 MEDLINE on STN
AN **90176799** MEDLINE
DN PubMed ID: 1689880
TI Role of gamma-**glutamyltranspeptidase** and beta-lyase in the nephrotoxicity of hexachloro-1,3-butadiene and methyl mercury in mice.

AU de Ceaurriz J; Ban M
CS Institut National de Recherche et de Securite, Vandoeuvre, France.
SO Toxicology letters, (1990 Feb) 50 (2-3) 249-56.
Journal code: 7709027. ISSN: 0378-4274.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199004
ED Entered STN: 19900601
Last Updated on STN: 19960129
Entered Medline: 19900410
AB Male Swiss OF1 mice received a single oral dose of either 80 mg/kg hexachloro-1,3-butadiene (HCBD) or 80 mg/kg methyl mercury (MeHg). Examination of cryostat kidney sections stained for alkaline phosphatase (APP) revealed damage to about 50% of the proximal tubules after 8 h. Pretreatment with the gamma-glutamyltranspeptidase (gamma-GT) inactivator AT-125 (Acivin, 50 mg/kg i.p., plus 50 mg/kg p.o., reduced the number of damaged tubules by 59 and 58% in mice treated with HCBD and MeHg, respectively. Pretreatment with the two beta-lyase inhibitors, amino-oxyacetic acid (AOAA, 3 x 100 mg/kg p.o.) and DL-propargylglycine (PPG, 300 mg/kg i.p. plus 300 mg/kg p.o.), reduced HCBD nephrotoxicity by 46 and 59%, respectively, but did not protect against MeHg nephrotoxicity. The results support a role for gamma-GT and beta-lyase in the mouse renal toxicity of HCBD and implicate gamma-GT but not beta-lyase in MeHg-induced nephrotoxicity in mice.
CT Alkaline Phosphatase: ME, metabolism
*Alkynes
Aminooxyacetic Acid: PD, pharmacology
Animals
*Butadienes: TO, toxicity
Glycine: AA, analogs & derivatives
Glycine: PD, pharmacology
Isoxazoles: PD, pharmacology
*Kidney Failure, Acute: CI, chemically induced
*Kidney Tubular Necrosis, Acute: CI, chemically induced
Kidney Tubular Necrosis, Acute: EN, enzymology
Kidney Tubular Necrosis, Acute: PC, prevention & control
Kidney Tubules, Proximal: DE, drug effects
Kidney Tubules, Proximal: EN, enzymology
*Lyases: AI, antagonists & inhibitors
Lyases: ME, metabolism
*Methylmercury Compounds: TO, toxicity
Mice
Pargyline: AA, analogs & derivatives
Pargyline: PD, pharmacology
Staining and Labeling
*gamma-Glutamyltransferase: AI, antagonists & inhibitors
gamma-Glutamyltransferase: ME, metabolism
RN 52583-41-2 (acivicin); 555-57-7 (Pargyline); 56-40-6 (Glycine); 64165-64-6 (propargylglycine); 645-88-5 (Aminooxyacetic Acid); 87-68-3 (hexachlorobutadiene)
CN 0 (Alkynes); 0 (Butadienes); 0 (Isoxazoles); 0 (Methylmercury Compounds); EC 2.3.2.2 (gamma-Glutamyltransferase); EC 3.1.3.1 (Alkaline Phosphatase); EC 4. (Lyases)

L25 ANSWER 6 OF 6 MEDLINE on STN
AN 88322348 MEDLINE
DN PubMed ID: 2901150
TI Effects of AT-125 on the nephrotoxicity of hexachloro-1,3-butadiene in rats.
AU Davis M E
CS Department of Pharmacology and Toxicology, West Virginia University, Morgantown 26506.

NC S01-R054
SO Toxicology and applied pharmacology, (1988 Aug) 95 (1) 44-52.
Journal code: 0416575. ISSN: 0041-008X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198809
ED Entered STN: 19900308
Last Updated on STN: 19950206
Entered Medline: 19880926
AB The role of **gamma-glutamyl transpeptidase** (**gamma-GTP**) in the nephrotoxicity of hexachloro-1,3-butadiene (HCBD) was studied using male Sprague-Dawley rats pretreated with **AT-125** (**Acivicin**; L-(alpha S, 5S)-alpha-amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid). Inhibition of **gamma-GTP** by more than 95% did not affect urine output, glomerular filtration rate, or tubular reabsorption of filtrate, sodium, or glucose. Nephrotoxicity observed during the first 24 hr after HCBD was not decreased by inhibition of **gamma-GTP** and beyond 24 hr nephrotoxicity was increased, rather than decreased, in the **AT-125**-pretreated group. HCBD impairs glucose reabsorption and this was greatly increased in the **AT-125**-pretreated group, indicating that function of the initial segment of the nephron is impaired by HCBD. Since inhibition of **gamma-GTP** did not protect against HCBD nephrotoxicity, it is concluded that **gamma-GTP** inhibition does not limit the formation of metabolites(s) which cause HCBD nephrotoxicity. Therefore, distribution of gamma-**glutamyltranspeptidase** does not account for the selective nephrotoxicity of hexachloro-1,3-butadiene.
CT Check Tags: Male
Animals
***Butadienes: AI, antagonists & inhibitors**
Butadienes: ME, metabolism
Butadienes: TO, toxicity
Glycosuria: CI, chemically induced
Glycosuria: ME, metabolism
*Isoxazoles: PD, pharmacology
Kidney Diseases: CI, chemically induced
***Kidney Diseases: EN, enzymology**
Kidney Function Tests
*Oxazoles: PD, pharmacology
Rats
Rats, Inbred Strains
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
Urine
***gamma-Glutamyltransferase: AI, antagonists & inhibitors**
gamma-Glutamyltransferase: ME, metabolism
RN **52583-41-2 (acivicin)**; 87-68-3 (hexachlorobutadiene)
CN 0 (Butadienes); 0 (Isoxazoles); 0 (Oxazoles); **EC 2.3.2.2** (gamma-**Glutamyltransferase**)

=> d all l30 tot

L30 ANSWER 1 OF 16 MEDLINE on STN
AN **2002078526** MEDLINE
DN PubMed ID: 11805394
TI Isolated liver perfusion permits administration of high doses of chemotherapeutic agents. Comparison with hepatic artery infusion.
AU Thorlacius H; Larmark M; Randell M; Hultberg B; Jeppsson B
CS Department of Surgery, Malmo University Hospital, Malmo, Sweden.
SO European surgical research. Europaische chirurgische Forschung. Recherches chirurgicales europeennes, (**2001 Sep-Dec**) 33 (5-6) 342-7.

Journal code: 0174752. ISSN: 0014-312X.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200204
ED Entered STN: 20020128
Last Updated on STN: 20020410
Entered Medline: 20020409
AB Tumor cells are dependent on glutamine metabolism and **acivicin**, which is a selective glutamine antagonist, has been shown to effectively retard tumor growth in several malignancies. However, systemic treatment with **acivicin** is associated with significant side effects. The purpose of the present study was to examine whether use of an in vivo isolated liver perfusion model may allow administration of lethal doses of **acivicin** and compare it to regional infusion of **acivicin** in the hepatic artery. Five days after tumor inoculation, **acivicin** was administered by an isolated liver perfusion model or by regional infusion via the hepatic artery. It was found that regional infusion of **acivicin** (5 and 10 mg/kg) via the hepatic artery caused systemic illness and diarrhea, and all animals in this group died within 3 days. In contrast, we observed no signs of systemic illness, diarrhea or hepatocellular injury in rats receiving isolated liver perfusion with or without **acivicin** (10 mg/kg) administration. Noteworthy, we found that isolated perfusion with **acivicin** reduced the glutamine content in liver tumors by 39% compared to perfusion with control medium. In line with this, it was found that isolated perfusion with **acivicin** (10 mg/kg) inhibited tumor growth in the liver. Taken together, this study suggests that application of the isolated liver perfusion model avoids the toxic and lethal effects of high doses of chemotherapy, herein **acivicin**, and may provide a useful approach to treat liver tumors in vivo.

CT Check Tags: Comparative Study; Male
***Adenocarcinoma: DT, drug therapy**
Adenocarcinoma: ME, metabolism
Adenocarcinoma: PA, pathology
Animals
***Antineoplastic Agents: AD, administration & dosage**
Glutamine: ME, metabolism
Hepatic Artery
Infusions, Intra-Arterial
***Isoxazoles: AD, administration & dosage**
Isoxazoles: TU, therapeutic use
***Liver Circulation**
***Liver Neoplasms, Experimental: DT, drug therapy**
Liver Neoplasms, Experimental: ME, metabolism
Liver Neoplasms, Experimental: PA, pathology
***Perfusion, Regional**
Rats
Rats, Inbred WF
Research Support, Non-U.S. Gov't
Treatment Outcome
gamma-Glutamyltransferase: AI, antagonists & inhibitors
RN **52583-41-2 (acivicin)**; 56-85-9 (Glutamine)
CN 0 (Antineoplastic Agents); 0 (Isoxazoles); **EC 2.3.2.2 (gamma-Glutamyltransferase)**

L30 ANSWER 2 OF 16 MEDLINE on STN
AN **2002023208** MEDLINE
DN PubMed ID: 11453733
TI Serotonergic neurotoxicity of 3,4-(+/-)-methylenedioxyamphetamine and 3,4-(+/-)-methylendioxymethamphetamine (ecstasy) is potentiated by inhibition of **gamma-glutamyl transpeptidase.**
AU Bai F; Jones D C; Lau S S; Monks T J
CS Center for Cellular and Molecular Toxicology, College of Pharmacy,

University of Texas at Austin, Austin, Texas 78712-1074, USA.
NC DA 108326 (NIDA)
SO Chemical research in toxicology, (2001 Jul) 14 (7) 863-70.
Journal code: 8807448. ISSN: 0893-228X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200112
ED Entered STN: 20020121
Last Updated on STN: 20020121
Entered Medline: 20011204
AB Reactive metabolites play an important role in 3,4-(+/-)-methylenedioxyamphetamine (MDA) and 3,4-(+/-)-methylenedioxymethamphetamine (MDMA; ecstasy)-mediated serotonergic neurotoxicity, although the specific identity of such metabolites remains unclear. 5-(Glutathion-S-yl)-alpha-methyldopamine (5-GSyl-alpha-MeDA) is a serotonergic neurotoxicant found in the bile of MDA-treated rats. The brain uptake of 5-GSyl-alpha-MeDA is decreased by glutathione (GSH), but sharply increases in animals pretreated with **acivicin**, an inhibitor of **gamma-glutamyl transpeptidase** (**gamma-GT**) suggesting competition between intact 5-GSyl-alpha-MeDA and GSH for the putative GSH transporter. **gamma-GT** is enriched in blood-brain barrier endothelial cells and is the only enzyme known to cleave the gamma-glutamyl bond of GSH. We now show that pretreatment of rats with **acivicin** (18 mg/kg, ip) inhibits brain microvessel endothelial **gamma-GT** activity by 60%, and potentiates MDA- and MDMA-mediated depletions in serotonin (5-HT) and 5-hydroxylindole acidic acid (5-HIAA) concentrations in brain regions enriched in 5-HT nerve terminal axons (striatum, cortex, hippocampus, and hypothalamus). In addition, glial fibrillary acidic protein (GFAP) expression increases in the striatum of **acivicin** and MDA (10 mg/kg) treated rats, but remains unchanged in animals treated with just MDA (10 mg/kg). Inhibition of endothelial cell **gamma-GT** at the blood-brain barrier likely enhances the uptake into brain of thioether metabolites of MDA and MDMA, such as 5-(glutathion-S-yl)-alpha-MeDA and 2,5-bis-(glutathion-S-yl)-alpha-MeDA, by increasing the pool of thioether conjugates available for uptake via the intact GSH transporter. The data indicate that thioether metabolites of MDA and MDMA contribute to the serotonergic neurotoxicity observed following peripheral administration of these drugs.
CT Check Tags: Male
3,4-Methylenedioxyamphetamine: AD, administration & dosage
3,4-Methylenedioxyamphetamine: AI, antagonists & inhibitors
*3,4-Methylenedioxyamphetamine: TO, toxicity
Administration, Cutaneous
Animals
*Brain: DE, drug effects
Brain: ME, metabolism
Endothelium: ME, metabolism
Enzyme Inhibitors: PD, pharmacology
Humans
*Isoxazoles: PD, pharmacology
Models, Molecular
N-Methyl-3,4-methylenedioxyamphetamine: AD, administration & dosage
N-Methyl-3,4-methylenedioxyamphetamine: AI, antagonists & inhibitors
*N-Methyl-3,4-methylenedioxyamphetamine: TO, toxicity
Neurotoxicity Syndromes
Neurotransmitters: AN, analysis
Rats
Rats, Sprague-Dawley
Research Support, U.S. Gov't, P.H.S.
Serotonin: ME, metabolism
Serotonin Agents: AD, administration & dosage
*Serotonin Agents: TO, toxicity

***gamma-Glutamyltransferase: AI, antagonists & inhibitors**
gamma-Glutamyltransferase: ME, metabolism
RN 42542-10-9 (N-Methyl-3,4-methylenedioxyamphetamine); 4764-17-4 (3,4-Methylenedioxyamphetamine); 50-67-9 (Serotonin); **52583-41-2 (acivicin)**
CN 0 (Enzyme Inhibitors); 0 (Isoxazoles); 0 (Neurotransmitters); 0 (Serotonin Agents); **EC 2.3.2.2 (gamma-Glutamyltransferase)**

L30 ANSWER 3 OF 16 MEDLINE on STN
AN **2001146599** MEDLINE
DN PubMed ID: 11194048
TI Biliary glutathione secretion in male single comb white leghorn chickens after inhibition of **gamma-glutamyl transpeptidase.**
AU Song Z; Bottje W G; Cawthon D; Beers K
CS Department of Poultry Science, University of Arkansas, Fayetteville 72701, USA.
SO Poultry science, **(2000 Dec)** 79 (12) 1829-32.
Journal code: 0401150. ISSN: 0032-5791.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200103
ED Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010315
AB The amount of hepatic export of glutathione into bile and the importance of **gamma-glutamyl transpeptidase** (gammaGT) activity for catabolizing glutathione in the bile duct, have not been reported previously for domestic fowl. Therefore, the primary objective of this study was to establish baseline values of biliary glutathione, and a secondary objective was to investigate the effect of **acivicin (AT-125**; a gammaGT inhibitor) on biliary glutathione in the chicken. Cannulae were placed in the carotid artery (to measure blood pressure) and into the left bile duct of anesthetized male Single Comb White Leghorn (SCWL) chickens (n = 5; 17 to 18 wk). The right bile duct was clamped between the liver and gall bladder. Bile samples were collected at 15-min intervals into microcentrifuge tubes (on ice) containing serine borate and iodoacetic acid to prevent glutathione oxidation. After two samples were obtained to establish baseline values, retrograde infusion of **AT-125** (30 microLmol/kg BW) was given to inhibit gammaGT activity in the biliary tree. Systemic blood pressure of the birds remained above 100 mm Hg throughout each experiment (90 to 120 min). Bile flow did not change significantly during the experiment and ranged between 0.15+/-0.03 and 0.20+/-0.07 mL/15 min per kg BW. Baseline biliary secretion values of reduced glutathione (GSH), oxidized glutathione (GSSG), and total glutathione (TGSH) were 4.6, 5.9, and 17 nmol/min per kg BW. After **AT-125** infusion, biliary GSH levels increased from 15 to 31 nmol/min per kg BW, indicating that considerable gammaGT-mediated catabolism of GSH occurred in the biliary tree of SCWL males. These results indicate that considerable turnover of GSH in the livers of domestic chickens is due to biliary excretion and that substantial recovery of GSH occurs through activity of gammaGT in the biliary tree.
CT Check Tags: Male
Animals
*Bile: SE, secretion
Bile Ducts: PH, physiology
Body Weight
*Chickens: PH, physiology
Constriction
*Enzyme Inhibitors: PD, pharmacology
*Glutathione: SE, secretion
Isoxazoles: PD, pharmacology

Liver: ME, metabolism
Oxidation-Reduction
***gamma-Glutamyltransferase: AI, antagonists & inhibitors**
gamma-Glutamyltransferase: ME, metabolism
RN **52583-41-2 (acivicin)**; 70-18-8 (Glutathione)
CN 0 (Enzyme Inhibitors); 0 (Isoxazoles); **EC 2.3.2.2** (**gamma-Glutamyltransferase**)

L30 ANSWER 4 OF 16 MEDLINE on STN
AN **97053363** MEDLINE
DN PubMed ID: 8897875
TI Dynamic aspects of glutathione and nitric oxide metabolism in endotoxemic rats.
AU Minamiyama Y; Takemura S; Koyama K; Yu H; Miyamoto M; Inoue M
CS Department of Biochemistry, Osaka City University Medical School, Japan.
SO American journal of physiology, (**1996 Oct**) 271 (4 Pt 1) G575-81.
Journal code: 0370511. ISSN: 0002-9513.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199612
ED Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961216
AB Glutathione is one of the most abundant thiols in mammalian tissues and plays important roles in the defense mechanism and detoxification of various metabolites, such as reactive xenobiotics and free radicals. Nitric oxide (NO) readily reacts with thiol compounds, thereby generating chemically stable S-nitrosothiols. Although endotoxin has been known to induce NO synthase in various organs, particularly liver and spleen, and enhances the production of NO, correlation between NO and glutathione metabolism in endotoxemic subjects remains to be elucidated. The present work examines the changes in NO and glutathione metabolism in endotoxemic rats. Administration of lipopolysaccharide (LPS) markedly decreased the glutathione levels in plasma and bile, whereas it decreased the hepatic level only slightly. NG-nitro-L-arginine (L-NNA), a NO synthase inhibitor, inhibited the LPS-induced decrease of glutathione in plasma and bile. Administration of LPS increased the biliary levels of **gamma-glutamyl transpeptidase (gamma-GTP)** without affecting its thiol levels. **Acivicin**, a **gamma-GTP** inhibitor, inhibited the LPS-induced decrease of glutathione in plasma and bile without affecting its hepatic levels. Analysis with the use of L-buthionine sulfoximine revealed that the turnover of hepatic glutathione significantly increased in LPS-treated rats by some L-NNA-inhibitable mechanism. These results suggest that endotoxin might enhance the NO production in the liver and other tissues and significantly modulate the interorgan metabolism of reduced glutathione.
CT Check Tags: Male
Animals
*Bile: ME, metabolism
Buthionine Sulfoximine: PD, pharmacology
***Endotoxemia: ME, metabolism**
*Endotoxins: PD, pharmacology
Enzyme Inhibitors: PD, pharmacology
*Glutathione: ME, metabolism
Isoxazoles: PD, pharmacology
*Lipopolysaccharides: PD, pharmacology
*Liver: ME, metabolism
*Nitric Oxide: ME, metabolism
Pancreas: ME, metabolism
Rats
Rats, Wistar
gamma-Glutamyltransferase: AI, antagonists & inhibitors
gamma-Glutamyltransferase: ME, metabolism

RN 10102-43-9 (Nitric Oxide); 5072-26-4 (Buthionine Sulfoximine); **52583-41-2 (acivicin)**; 70-18-8 (Glutathione)
CN 0 (Endotoxins); 0 (Enzyme Inhibitors); 0 (Isoxazoles); 0 (Lipopolysaccharides); **EC 2.3.2.**
2 (gamma-Glutamyltransferase)

L30 ANSWER 5 OF 16 MEDLINE on STN
AN **96362741** MEDLINE
DN PubMed ID: 8729948
TI A phase I study of **acivicin** in refractory pediatric solid tumors. A Pediatric Oncology Group study.
AU Baruchel S; Bernstein M; Whitehead V M; Devine S; Bell B; Dubowy R; Grier H; Kretschmar C; Langevin A M; Vietti T
CS McGill University, Montreal, Canada.
NC CA-20549 (NCI)
CA-28383 (NCI)
CA-33587 (NCI)
+
SO Investigational new drugs, **(1995)** 13 (3) 211-6.
Journal code: 8309330. ISSN: 0167-6997.
CY United States
DT (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199610
ED Entered STN: 19961106
Last Updated on STN: 19970203
Entered Medline: 19961021
AB Forty-two patients with progressive solid tumors and brain tumors were entered in this Phase I study of the glutamine antagonist **acivicin** given intravenously over thirty minutes daily for five days. The major toxicities encountered were myelosuppression and central nervous system toxicity (nightmares and somnolence). The maximum tolerated dosage on this schedule was 26 mg/M2 daily for five days. Six patients including three patients with brain tumor had stable disease.
CT Adolescent
*Antimetabolites, Antineoplastic: AE, adverse effects
Antimetabolites, Antineoplastic: TU, therapeutic use
Child
Child, Preschool
Drug Resistance, Neoplasm
*Enzyme Inhibitors: AE, adverse effects
Enzyme Inhibitors: TU, therapeutic use
Humans
Injections, Intravenous
*Isoxazoles: AE, adverse effects
Isoxazoles: TU, therapeutic use
***Neoplasms: DT, drug therapy**
Research Support, U.S. Gov't, P.H.S.
Tumor Cells, Cultured: DE, drug effects
gamma-Glutamyltransferase: AI, antagonists & inhibitors
RN **52583-41-2 (acivicin)**
CN 0 (Antimetabolites, Antineoplastic); 0 (Enzyme Inhibitors); 0 (Isoxazoles); **EC 2.3.2.2**
(gamma-Glutamyltransferase)

L30 ANSWER 6 OF 16 MEDLINE on STN
AN **96303179** MEDLINE
DN PubMed ID: 8723029
TI Prevention of diabetes in the spontaneously diabetic BB rat by the glutamine antimetabolite **acivicin**.
AU Misra M; Duguid W P; Marliss E B
CS McGill Nutrition and Food Science Centre, Royal Victoria Hospital, Montreal, QC, Canada.

SO Canadian journal of physiology and pharmacology, (1996 Feb) 74 (2) 163-72.
Journal code: 0372712. ISSN: 0008-4212.
CY Canada
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199704
ED Entered STN: 19970414
Last Updated on STN: 19980206
Entered Medline: 19970403
AB The autoimmune syndrome of the BB rat is associated with a marked increase in glutamine (Gln) metabolism in immune system cells of both diabetes-prone (BBdp) and diabetic (BBd) rats. To test whether inhibition of Gln metabolism prevents diabetes, 17 BBdp received **acivicin** (1 mg/kg) and 17 received saline subcutaneously every 2 days from age 48 days until diabetes onset or age 186 days. Twenty-seven non-diabetes-prone (BBn) rats served as controls. **Acivicin** caused some growth effects and a macrocytic anemia, but no other clinical or biochemical side effects. Only one **acivicin**-treated BBdp became diabetic (age 158 days), compared with saline-treated rats, of which 10 became diabetic and 2 became glucose intolerant ($p < 0.001$). Insulitis was moderate to severe in 88% of the saline-treated BBdp rats, but minimal in most **acivicin**-treated BBdp rats. Liver glutamine and glutamate tended to be higher in **acivicin**- than saline-treated BBdp rats. **Acivicin** caused no change in the proportions of T or B lymphocytes, NK cells, or macrophage phenotypes in spleen or blood; all BBdp rats were typically lymphopenic. Mitogenic responses of splenocytes in vitro were not affected. The results are consistent with the hypothesis that **acivicin**, by interfering with Gln metabolism, "targets" activated cells of the immune system and thereby attenuates the process and prevents overt diabetes, without major disturbance of Gln levels or generalized immunosuppression. This prevention is not due to a nutritional-growth retardation effect, as diabetes was prevented in females that showed no such effect.
CT Check Tags: Comparative Study; Female; Male
Animals
Blood Cell Count
***Diabetes Mellitus, Type 1: PC, prevention & control**
Drug Interactions
Enzyme Inhibitors: PD, pharmacology
*Enzyme Inhibitors: TU, therapeutic use
Glucose Tolerance Test
Glutamic Acid: ME, metabolism
*Glutamine: ME, metabolism
Ionomycin: PD, pharmacology
Isoxazoles: PD, pharmacology
*Isoxazoles: TU, therapeutic use
Lymphocyte Subsets: DE, drug effects
Rats
Rats, Inbred BB
Research Support, Non-U.S. Gov't
Spleen: CY, cytology
Spleen: DE, drug effects
Tetradecanoylphorbol Acetate: PD, pharmacology
***gamma-Glutamyltransferase: AI, antagonists & inhibitors**
RN 16561-29-8 (Tetradecanoylphorbol Acetate); **52583-41-2 (acivicin)**; 56-85-9 (Glutamine); 56-86-0 (Glutamic Acid); 56092-81-0 (Ionomycin)
CN 0 (Enzyme Inhibitors); 0 (Isoxazoles); **EC 2.3.2.2** (gamma-**Glutamyltransferase**)

L30 ANSWER 7 OF 16 MEDLINE on STN
AN **96231934** MEDLINE
DN PubMed ID: 8632493
TI **gamma-Glutamyl transpeptidase** mediation of tumor glutathione utilization in vivo.

AU Hochwald S N; Harrison L E; Rose D M; Anderson M; Burt M E
CS Department of Surgery, Surgical Metabolism Laboratory, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA.
SO Journal of the National Cancer Institute, (1996 Feb 21) 88 (3-4) 193-7.
Journal code: 7503089. ISSN: 0027-8874.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199607
ED Entered STN: 19960715
Last Updated on STN: 20000303
Entered Medline: 19960702
AB BACKGROUND: Glutathione is a tripeptide used by cells to protect against oxidative and free radical damage. It may also be involved in biochemical mechanisms that cause some tumors to become resistant to anticancer drugs. **gamma-Glutamyl transpeptidase** (GGTP) is a membrane-bound enzyme that cleaves extracellular glutathione, providing cells with amino acids necessary for intracellular synthesis of this compound. Increased expression of GGTP has been found in a number of human tumors; however, few studies have examined the contribution of GGTP to tumor glutathione metabolism in vivo. PURPOSE: Our goals were to study the utilization of host glutathione by 3-methylcholanthrene (MCA)-induced sarcomas grown in rats and to evaluate the involvement of tumor GGTP in this process. METHODS: The left ovaries of 21 female Fischer 344 rats were isolated by laparotomy and placed in subcutaneous positions through stab wounds in the abdominal wall. A 3-mm cube of MCA sarcoma was then sutured to each of the isolated ovaries. The MCA implants obliterated the ovarian tissue, yielding isolated tumors with one arterial supply (the ovarian artery) and one draining vein (the ovarian vein, referred to as the tumor vein). After 2 weeks of tumor growth, blood was drawn from the tumor vein, the inferior vena cava (IVC), and the aorta of 16 animals. Glutathione and cysteine concentrations in plasma samples from this blood were determined by high-performance liquid chromatography and used to calculate glutathione and cysteine utilization ratios for the tumor and the systemic circulations ([(concentration aorta-concentration tumor vein)/concentration aorta] x 100 and [(concentration aorta-concentration IVC)/concentration aorta] x 100, respectively). The utilization ratios from these control animals were compared with those from **acivicin** (**AT-125**; an irreversible GGTP inhibitor)-treated rats (the remaining five animals). Data are presented as mean +/- standard deviation; reported P values are from two-tailed tests of statistical significance. RESULTS: In the control animals, glutathione and cysteine concentrations were significantly lower in the tumor vein (3.55 +/- 1.9 and 5.69 +/- 2.8 microM, respectively) and in the IVC (5.65 +/- 2.3 and 7.17 +/- 2.4 microM, respectively) than in the artery (12.48 +/- 5.7 and 12.33 +/- 5.9 microM, respectively; all P values < .05). In addition, the glutathione utilization ratio was significantly higher for the tumor circulation than for the systemic circulation (69% +/- 14% versus 52% +/- 14%; P < .003). The combined glutathione and cysteine utilization ratio was also significantly higher for the tumor circulation than for the systemic circulation (116% +/- 35% versus 88% +/- 28%; P < .02). Treatment with **AT-125** lowered the tumor glutathione utilization ratio significantly (45% +/- 12% for treated animals versus 69% +/- 14% for control animals; P < .005). CONCLUSIONS: Our results show that glutathione and cysteine in the host circulation are used by MCA sarcomas. The significant reduction in tumor utilization of serum glutathione after treatment with **AT-125**, a GGTP inhibitor, indicates that GGTP is important in tumor glutathione metabolism.
CT Check Tags: Female
Animals
Cysteine: ME, metabolism
Enzyme Inhibitors: PD, pharmacology
*Glutathione: ME, metabolism

Isoxazoles: PD, pharmacology
Methylcholanthrene
Rats
Rats, Inbred F344
Sarcoma, Experimental: EN, enzymology
***Sarcoma, Experimental: ME, metabolism**
gamma-Glutamyltransferase: AI, antagonists & inhibitors
***gamma-Glutamyltransferase: ME, metabolism**
RN 52-90-4 (Cysteine); **52583-41-2 (acivicin)**; 56-49-5 (Methylcholanthrene); 70-18-8 (Glutathione)
CN 0 (Enzyme Inhibitors); 0 (Isoxazoles); **EC 2.3.2.2** (gamma-**Glutamyltransferase**)

L30 ANSWER 8 OF 16 MEDLINE on STN
AN **96063893** MEDLINE
DN PubMed ID: 8519693
TI Inhibition of **gamma-glutamyl transpeptidase** activity at the surface of human myeloid cells is correlated with macrophage maturation and transforming growth factor beta production.
AU Bauvois B; Laouar A; Rouillard D; Wietzerbin J
CS Unite 365 INSERM-Institut Curie, Paris, France.
SO Cell growth & differentiation : molecular biology journal of the American Association for Cancer Research, **(1995 Sep)** 6 (9) 1163-70.
Journal code: 9100024. ISSN: 1044-9523.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199601
ED Entered STN: 19960219
Last Updated on STN: 19970203
Entered Medline: 19960125
AB The protease **gamma-glutamyl transpeptidase** (**gamma-GT**) activity was detected at the surface of human blood granulocytes and monocytes and myeloblastic HL-60 and monoblastic U937 leukemia cell lines using an enzymatic assay (cleavage of gamma-glu-p-nitroanilide and inhibition by the specific irreversible inhibitor of **gamma-GT**, i.e., **acivicin**).
Flow cytometric analysis of **gamma-GT** expression and detection of a 2.4-kb **gamma-GT** mRNA species by Northern blot analysis confirmed the presence of **gamma-GT** in cells of the monocytic-granulocytic lineage.
Differentiation of HL-60, U937 cells, and blood monocytes along the macrophage pathway or granulocytic maturation of HL-60 cells was accompanied by an increase in **gamma-GT** mRNA levels without modulation of cell surface **gamma-GT** activity and protein. When added to leukemic cell cultures, **acivicin** produced a dose- and time-dependent inhibitory growth effect associated with the induction of morphological features characteristic of macrophage maturation and enhanced surface expression of phenotypic markers CD11b and CD71 characteristic of monocyte development. When cultured in the presence of **acivicin**, freshly isolated monocytes also underwent characteristic changes in morphology and antigenic phenotype (increase in CD71 and HLA-DR class II) consistent with their differentiation into macrophages. In parallel, a marked production of latent transforming growth factor (TGF)-beta was observed in supernatants of cells cultured with **acivicin**, although TGF-beta 1 mRNA species were expressed in these cells at a level almost similar to that in unstimulated cell cultures. Moreover, **acivicin**-treated cells still differentiated into macrophages in the presence of a neutralizing antibody to TGF-beta 1/beta 2.(ABSTRACT TRUNCATED AT 250 WORDS)
CT Check Tags: Comparative Study
Cell Aging: PH, physiology
Cell Differentiation: PH, physiology
Cell Membrane: EN, enzymology
Cells, Cultured

Humans
*Leukemia, Monocytic, Acute: EN, enzymology
Leukemia, Monocytic, Acute: PA, pathology
*Leukemia, Myeloid: EN, enzymology
Leukemia, Myeloid: PA, pathology
*Macrophages: CY, cytology
Research Support, Non-U.S. Gov't
*Transforming Growth Factor beta: BI, biosynthesis
Tumor Cells, Cultured
*gamma-Glutamyltransferase: AI, antagonists & inhibitors
CN 0 (Transforming Growth Factor beta); EC 2.3.
2.2 (gamma-Glutamyltransferase)

L30 ANSWER 9 OF 16 MEDLINE on STN
AN 95042327 MEDLINE
DN PubMed ID: 7954424
TI Inhibition of gamma-glutamyl transpeptidase activity by acivicin in vivo protects the kidney from cisplatin-induced toxicity.
AU Hanigan M H; Gallagher B C; Taylor P T Jr; Large M K
CS Department of Cell Biology, University of Virginia Health Sciences Center, Charlottesville 22908.
NC CA 57530 (NCI)
P30-HD28934 (NICHD)
SO Cancer research, (1994 Nov 15) 54 (22) 5925-9.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199412
ED Entered STN: 19950110
Last Updated on STN: 19950110
Entered Medline: 19941202
AB Cisplatin [cis-dichlorodiammineplatinum(II)] is a widely used chemotherapeutic drug that is toxic to the proximal tubule cells of the kidney. gamma-Glutamyl transpeptidase (GGT) is localized to the luminal surface of the renal proximal tubules. GGT catalyzes the initial step in the metabolism of glutathione-conjugated drugs to mercapturic acids, some of which are severely nephrotoxic. We proposed that the nephrotoxicity of cisplatin was dependent on the cleavage of a cisplatin-glutathione conjugate by GGT. To test this hypothesis, renal GGT activity was blocked in male Sprague-Dawley rats by acivicin, a non-competitive inhibitor of GGT. Treatment with cisplatin alone caused extensive acute necrosis of the proximal tubules, but the proximal tubule cells appeared normal in rats treated with acivicin prior to cisplatin. Blood urea nitrogen and serum creatinine levels confirmed the protective effect of acivicin. Glutathione is a physiological substrate for GGT. Administration of an 83-fold excess of glutathione 30 min prior to cisplatin also inhibited cisplatin-induced nephrotoxicity. These data provide important new evidence that a large bolus of glutathione blocks the nephrotoxicity of cisplatin by competitively inhibiting GGT. These results indicate that cisplatin is conjugated to glutathione in vivo. The platinum-glutathione conjugate is nontoxic until metabolized by the proximal tubule cells. Formation of the nephrotoxic derivative of cisplatin requires GGT activity.
CT Check Tags: Male
Animals
Blood Urea Nitrogen
Body Weight: DE, drug effects
Cisplatin: AE, adverse effects
*Cisplatin: AI, antagonists & inhibitors
Cisplatin: ME, metabolism
Creatinine: BL, blood

Eating
Glutathione: ME, metabolism
*Isoxazoles: PD, pharmacology
*Kidney: DE, drug effects
Kidney: EN, enzymology
Kidney: PA, pathology
Kidney Tubules, Proximal: DE, drug effects
Rats
Rats, Sprague-Dawley
Research Support, U.S. Gov't, P.H.S.
*gamma-Glutamyltransferase: AI, antagonists & inhibitors
RN 15663-27-1 (Cisplatin); 52583-41-2 (acivicin); 60-27-5 (Creatinine); 70-18-8 (Glutathione)
CN 0 (Isoxazoles); EC 2.3.2.2 (gamma-Glutamyltransferase)

L30 ANSWER 10 OF 16 MEDLINE on STN
AN 95017052 MEDLINE
DN PubMed ID: 7931622
TI Enzymatic barrier protects brain capillaries from leukotriene C4.
AU Black K L; Baba T; Pardridge W M
CS Brain Research Institute, University of California, Los Angeles Medical Center.
NC 1PO1NS25554 (NINDS)
1R01N532103
SO Journal of neurosurgery, (1994 Nov) 81 (5) 745-51.
Journal code: 0253357. ISSN: 0022-3085.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199411
ED Entered STN: 19941222
Last Updated on STN: 20000303
Entered Medline: 19941114
AB Leukotriene C4 (LTC4) increases vascular permeability in systemic, brain tumor, and ischemic brain capillaries, but not in normal brain capillaries. This study examines whether the abundance of gamma-glutamyl transpeptidase (gamma-GTP) in normal brain capillaries might act as an enzymatic barrier to vasoactive leukotrienes in the brain. Blood-brain barrier (BBB) permeability was determined by quantitative autoradiography using 14C-aminoisobutyric acid. Ischemia was produced by occluding the middle cerebral artery. Seventy-two hours after occlusion, gamma-GTP activity in ischemic brain disappeared, and LTC4 (4-micrograms total dose), which was infused into the carotid artery ipsilateral to the occlusion, selectively increased permeability, Ki, approximately twofold within core ischemic tissue and adjacent tissue, compared to vehicle alone in seven brains (15.53 +/- 6.03 vs. 7.29 +/- 3.36, $p < 0.05$, and 8.76 +/- 4.02 vs. 4.32 +/- 2.65, $p < 0.05$, respectively). No effect on BBB was seen in nonischemic brain tissue. Twenty-four hours postocclusion, gamma-GTP activity was still present, and LTC4 infusion did not increase permeability within ischemic tissue. However, inhibition of gamma-GTP with acivicin allowed LTC4 to increase permeability even 24 hours after occlusion in ischemic core and adjacent tissue compared to vehicle alone in seven brains (17.21 +/- 16.32 vs. 8.23 +/- 6.58, $p < 0.05$, and 11.78 +/- 7.96 vs. 4.56 +/- 1.93, $p < 0.01$, respectively). Acivicin almost completely blocked both the histochemical activity of gamma-GTP in brain capillaries and the metabolism of LTC4 in isolated bovine capillaries. These findings suggest that gamma-GTP may help normal brain capillaries resist the vasoactive effects of LTC4. In contrast, gamma-GTP is lost in injured brain capillaries, which allows LTC4 (in combination with other factors) to increase vascular permeability in ischemic brain and brain tumors.
CT Check Tags: Female

Animals
Antimetabolites: PD, pharmacology
Autoradiography
Blood-Brain Barrier: DE, drug effects
*Brain: BS, blood supply
Brain: EN, enzymology
Brain Ischemia: EN, enzymology
Brain Ischemia: PA, pathology
Brain Ischemia: PP, physiopathology
Capillaries: DE, drug effects
Capillaries: EN, enzymology
Capillary Permeability: DE, drug effects
Cattle
Isoxazoles: PD, pharmacology
Leukotriene C4: AI, antagonists & inhibitors
Leukotriene C4: ME, metabolism
*Leukotriene C4: PD, pharmacology
Rats
Rats, Wistar
Receptors, Leukotriene: DE, drug effects
Receptors, Leukotriene: ME, metabolism
Research Support, U.S. Gov't, P.H.S.
Time Factors
gamma-Glutamyltransferase: AI, antagonists & inhibitors
***gamma-Glutamyltransferase: PH, physiology**

RN 52583-41-2 (acivicin); 72025-60-6 (Leukotriene C4)
CN 0 (Antimetabolites); 0 (Isoxazoles); 0 (Receptors, Leukotriene); 0 (leukotriene C4 receptor); EC 2.3.2
.2 (gamma-Glutamyltransferase)

L30 ANSWER 11 OF 16 · MEDLINE on STN
AN 94274542 MEDLINE
DN PubMed ID: 7911799
TI Elimination of glutathione-induced protection from hyperbaric hyperoxia by **acivicin.**
AU Peacock M D; Schenk D A; Lawrence R A; Morgan J A; Jenkinson S G
CS Lung Metabolic Unit, University of Texas Health Science Center at San Antonio.
SO Journal of applied physiology (Bethesda, Md. : 1985), **(1994 Mar)** 76 (3) 1279-84.
Journal code: 8502536. ISSN: 8750-7587.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Space Life Sciences
EM 199407
ED Entered STN: 19940729
Last Updated on STN: 19950206
Entered Medline: 19940715
AB Glutathione (GSH) administered intraperitoneally significantly prolongs the time to initial seizure and survival time of rats exposed to hyperbaric hyperoxia (HBO). **Acivicin** is an antitumor antibiotic that is an inhibitor of **gamma-glutamyl transpeptidase** (**GGT**), an enzyme necessary for the breakdown and transport across cell membranes of GSH. To determine whether **acivicin** treatment alters GSH-induced protection from HBO, rats were dosed with 25 mg/kg of **acivicin** or vehicle 1 h before O2 exposure at an inspired O2 fraction of 1.0 at 4 ATA. Immediately before exposure, rats received GSH (1 mmol/kg) or vehicle. Time to seizure and time to death were recorded during exposure by direct observation. In separate groups of rats on the same dosing schedule, plasma GSH, renal **GGT**, and brain **GGT** were measured 15 min after the GSH injection without HBO exposure and 100 min after the beginning of HBO exposure. Renal **GGT** was decreased to 2.5% of control and brain **GGT** to 37% of control in the **acivicin** -dosed rats. Plasma GSH increased 3-fold in rats given **acivicin**

alone, 52-fold in rats given GSH alone, and 84-fold in rats receiving both acivicin and GSH. Rats dosed with GSH alone had significantly prolonged times to seizure and death compared with all other groups. Rats dosed with GSH after receiving acivicin were not protected from HBO despite the large increase in plasma GSH that occurred in these animals. GSH treatment did not increase tissue GSH in lung, liver, or brain at 160 or 200 min of exposure.(ABSTRACT TRUNCATED AT 250 WORDS)

CT Check Tags: Male
Animals
Brain: EN, enzymology
Brain Chemistry: DE, drug effects
***Glutathione: AI, antagonists & inhibitors**
Glutathione: ME, metabolism
Glutathione: PD, pharmacology
*Hyperbaric Oxygenation: AE, adverse effects
*Isoxazoles: PD, pharmacology
Kidney: EN, enzymology
Kidney: ME, metabolism
Lung: EN, enzymology
Lung: ME, metabolism
***Oxygen: AI, antagonists & inhibitors**
Oxygen: TO, toxicity
Rats
Rats, Sprague-Dawley
Research Support, U.S. Gov't, Non-P.H.S.
Seizures: CI, chemically induced
Seizures: PC, prevention & control
gamma-Glutamyltransferase: AI, antagonists & inhibitors
gamma-Glutamyltransferase: ME, metabolism

RN 52583-41-2 (acivicin); 70-18-8 (Glutathione); 7782-44-7 (Oxygen)
CN 0 (Isoxazoles); EC 2.3.2.2 (gamma-Glutamyltransferase)

L30 ANSWER 12 OF 16 MEDLINE on STN
AN 94219988 MEDLINE
DN PubMed ID: 7909430
TI Nephrotoxicity of 4-amino-3-S-glutathionylphenol and its modulation by metabolism or transport inhibitors.
AU Fowler L M; Foster J R; Lock E A
CS Zeneca Central Toxicology Laboratory, Alderley Park, Cheshire, UK.
SO Archives of toxicology, (1994) 68 (1) 15-23.
Journal code: 0417615. ISSN: 0340-5761.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199405
ED Entered STN: 19940606
Last Updated on STN: 19960129
Entered Medline: 19940524
AB The nephrotoxicity of 4-amino-3-S-glutathionylphenol (PAP-GSH), a known metabolite of 4-amino-phenol (PAP), was determined in male Fischer 344 rats. Administration of a single dose of 40 or 60 mumol kg-1 caused a marked elevation in blood urea nitrogen and an increase in the urinary excretion of glucose, protein and gamma-glutamyltransferase (GGT). These changes were associated with histological alterations in the proximal tubule, where at the lower dose the lesion was restricted to the S3 region of the proximal tubule in the medullary rays, while at the higher dose the lesion extended to affect the S3 region in both the medullary rays and the outer stripe of the outer medulla. Studies with [35S]-PAP-GSH at 40 mumol kg-1 showed selective retention of radioactivity in the kidney, relative to other organs 24 h after dosing and that some radioactivity was covalently bound to renal proteins. Pretreatment of animals with probenecid, an inhibitor of renal organic anion transport, or aminooxyacetic acid, an inhibitor of cysteine conjugate beta-lyase, had little or no effect on the toxicity. In contrast, pretreatment of animals

with acivicin, an inhibitor of gamma-glutamyltransferase , or co-administration of PAP-GSH with ascorbic acid almost completely protected against the nephrotoxicity. This protection was associated with a decreased concentration of radioactivity from [35S]-PAP-GSH in the kidneys and a decrease in the amount covalently bound to renal protein. Thus, the nephrotoxicity of PAP-GSH may be mediated by oxidation and further processing of the glutathione conjugate via gamma-glutamyltransferase.

CT Check Tags: Male
Aminooxyacetic Acid: PD, pharmacology
Animals
Ascorbic Acid: PD, pharmacology
Blood Urea Nitrogen
*Glutathione: AA, analogs & derivatives
Glutathione: ME, metabolism
Glutathione: PK, pharmacokinetics
Glutathione: TO, toxicity
Glycosuria: CI, chemically induced
Ion Transport
Isoxazoles: PD, pharmacology
*Kidney: DE, drug effects
Kidney: PA, pathology
Lyases: ME, metabolism
Oxidation-Reduction
Phenols: ME, metabolism
Phenols: PK, pharmacokinetics
*Phenols: TO, toxicity
Probenecid: PD, pharmacology
Proteinuria: CI, chemically induced
Rats
Rats, Inbred F344
Sulfur Radioisotopes: DU, diagnostic use
gamma-Glutamyltransferase: AI, antagonists & inhibitors
***gamma-Glutamyltransferase: ME, metabolism**
gamma-Glutamyltransferase: UR, urine

RN 129762-74-9 (4-amino-3-S-glutathionylphenol); 50-81-7 (Ascorbic Acid); 52583-41-2 (acivicin); 57-66-9 (Probenecid); 645-88-5 (Aminooxyacetic Acid); 70-18-8 (Glutathione)

CN 0 (Isoxazoles); 0 (Phenols); 0 (Sulfur Radioisotopes); EC 2.3.2.2 (gamma-Glutamyltransferase); EC 4. (Lyases)

L30 ANSWER 13 OF 16 MEDLINE on STN
AN 94164747 MEDLINE
DN PubMed ID: 7907080
TI Gamma-glutamyltranspeptidase expression regulates the growth-inhibitory activity of the anti-tumor prodrug gamma-L-glutaminyl-4-hydroxy-3-iodobenzene.
AU Prezioso J A; Hughey R P; Wang N; Damodaran K M; Bloomer W D
CS Department of Radiation Oncology, University of Pittsburgh School of Medicine, PA 15213.
NC DK26012 (NIDDK)
SO International journal of cancer. Journal international du cancer, (1994 Mar 15) 56 (6) 874-9.
Journal code: 0042124. ISSN: 0020-7136.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199404
ED Entered STN: 19940412
Last Updated on STN: 19980206
Entered Medline: 19940407
AB gamma-L-glutaminyl-4-hydroxy-3-iodobenzene (I-GHB), a novel iodinated analog of gamma-L-glutaminyl-4-hydroxybenzene (GHB), demonstrates greater anti-tumor activity in human and in murine melanoma cell lines. These

phenolic amides are substrates for gamma-**glutamyltranspeptidase** (GGTP; **E.C. 2.3.2.2**), a cell-membrane-associated ecto-enzyme which is elevated in a number of tumor systems. We now present data to show that the growth-inhibitory activity of I-GHB and GHB may be mediated via GGTP-catalyzed reactions. The growth-inhibitory activity of I-GHB and GHB in pigmented B16-BL6 melanoma cells was blocked significantly by rabbit anti-rat GGTP polyclonal antibodies. The combination of L-serine and sodium borate, a specific transition-state inhibitor of GGTP, as well as **acivicin**, a glutamine antagonist and irreversible GGTP inhibitor, inhibited the killing of BL6 cells by GHB and I-GHB. To further define the role of GGTP expression in the regulation of phenolic amide cytotoxicity, GGTP-negative Chinese hamster ovary cells (CHO-K1) were transfected with a functional rat renal cDNA representing the full-length GGTP transcript. I-GHB and GHB were significantly more cytotoxic in GGTP cDNA transfected Chinese hamster ovary (CHO-K1-GGTP) cells than in non-transfected CHO-K1 cells. The combination of L-serine and sodium borate blocked the cytotoxic activity of these pro-drugs and also inhibited GGTP-catalyzed formation of polymerized products from these phenolic amides in intact BL6 melanoma and CHO-K1-GGTP cells. Furthermore, melanin formation from GHB was not observed in non-transfected CHO-K1 cells lacking GGTP expression. The combined data strongly suggest that GGTP-catalyzed hydrolysis of the anti-tumor pro-drugs I-GHB and GHB to 4-aminophenols mediates the expression of antitumor activity.

CT Animals
Antineoplastic Agents: AI, antagonists & inhibitors
*Antineoplastic Agents: ME, metabolism
Antineoplastic Agents: PD, pharmacology
Borates: PD, pharmacology
CHO Cells: DE, drug effects
*CHO Cells: ME, metabolism
CHO Cells: PA, pathology
Cell Division
*Glutamine: AA, analogs & derivatives
Glutamine: AI, antagonists & inhibitors
Glutamine: ME, metabolism
Glutamine: PD, pharmacology
Glutathione: ME, metabolism
Hamsters
Hydrolysis
Isoxazoles: PD, pharmacology
Melanins: BI, biosynthesis
***Melanoma, Experimental: ME, metabolism**
Melanoma, Experimental: PA, pathology
Mice
Phenols: AI, antagonists & inhibitors
*Phenols: ME, metabolism
Phenols: PD, pharmacology
*Prodrugs: ME, metabolism
Prodrugs: PD, pharmacology
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
Serine: PD, pharmacology
Transfection
gamma-Glutamyltransferase: AI, antagonists & inhibitors
gamma-Glutamyltransferase: GE, genetics
***gamma-Glutamyltransferase: ME, metabolism**

RN 1330-43-4 (sodium borate); 147139-63-7 (gamma-glutaminyl-4-hydroxy-3-iodobenzene); **52583-41-2 (acivicin)**; 56-45-1 (Serine); 56-85-9 (Glutamine); 70-18-8 (Glutathione)

CN 0 (Antineoplastic Agents); 0 (Borates); 0 (Isoxazoles); 0 (Melanins); 0 (Phenols); 0 (Prodrugs); **EC 2.3.2.2** (gamma-**Glutamyltransferase**)

L30 ANSWER 14 OF 16 MEDLINE on STN

AN 94106631 MEDLINE
DN PubMed ID: 7904127
TI Bidirectional membrane transport of intact glutathione in Hep G2 cells.
AU Sze G; Kaplowitz N; Ookhtens M; Lu S C
CS Department of Medicine, University of Southern California School of Medicine, Los Angeles 90033.
NC DK-30312 (NIDDK)
DK-45334 (NIDDK)
SO American journal of physiology, (1993 Dec) 265 (6 Pt 1) G1128-34.
Journal code: 0370511. ISSN: 0002-9513.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199402
ED Entered STN: 19940218
Last Updated on STN: 19980206
Entered Medline: 19940208
AB Rat hepatocytes exhibit bidirectional carrier-mediated transport of reduced glutathione (GSH) across the plasma membrane. Transport of GSH has not been well characterized in human-derived cells. We examined Hep G2 cells as a possible human liver model for GSH homeostasis. Hep G2 cell GSH averaged 25.9 +/- 1.4 nmol/10(6) cells. When Hep G2 cells were incubated in buffer, no GSH appeared in the medium over 2 h. However, after pretreatment with **acivicin** to inhibit **gamma-glutamyl transpeptidase** activity, GSH efflux was unmasked and measured 30 +/- 4 pmol x 10(6) cells-1 x min-1, which is comparable to rat hepatocytes. GSH efflux was inhibited by sulfobromophthalein GSH adduct (BSP-GSH) and cystathionine, agents that inhibit sinusoidal efflux in the rat, and was stimulated by adenosine 3',5'-cyclic monophosphate-dependent agents. GSH uptake was measured after cells were pretreated with **acivicin** and buthionine sulfoximine to prevent breakdown of GSH and resynthesis of GSH from precursors, respectively. In the presence of 4 microCi/ml of [35S]GSH and 10 mM unlabeled GSH, GSH uptake was linear up to 45 min and did not require Na+ or Cl-. GSH uptake exhibited saturability with a maximal velocity of 4.15 +/- 0.23 nmol.mg-1 x 30 min-1, a Michaelis constant of 2.36 +/- 0.26 mM, and two interactive transport sites. BSP-GSH cis-inhibited GSH uptake in a dose-dependent manner with an inhibitory constant of 0.46 +/- 0.05 mM. Inhibition by BSP-GSH (1 mM) of GSH uptake was through a single inhibitor site and was overcome at > 10 mM GSH, which is consistent with competitive inhibition. Similar to the rat, 10 mM extracellular GSH trans-stimulated GSH efflux. These findings may be important in gaining better insights into GSH homeostasis in human liver cells.
CT Biological Transport
Bucladesine: PD, pharmacology
Cell Line
*Cell Membrane: ME, metabolism
Cholera Toxin: PD, pharmacology
*Glutathione: ME, metabolism
Glutathione: PD, pharmacology
Hepatoblastoma
Homeostasis
Humans
Isoxazoles: PD, pharmacology
Kinetics
*Liver: ME, metabolism
Liver Neoplasms
Research Support, U.S. Gov't, P.H.S.
Sulfobromophthalein: PD, pharmacology
Tumor Cells, Cultured
gamma-Glutamyltransferase: AI, antagonists & inhibitors
gamma-Glutamyltransferase: ME, metabolism
RN 297-83-6 (Sulfobromophthalein); 362-74-3 (Bucladesine); **52583-41-2**

(acivicin); 52682-84-5 ((sulfobromophthalein)glutathione conjugate); 70-18-8 (Glutathione); 9012-63-9 (Cholera Toxin)
CN 0 (Isoxazoles); EC 2.3.2.2 (gamma-Glutamyltransferase)

L30 ANSWER 15 OF 16 MEDLINE on STN
AN 90297270 MEDLINE
DN PubMed ID: 1972865
TI Glutathione catabolism by the ischemic rat kidney.
AU Slusser S O; Grotyohann L W; Martin L F; Scaduto R C Jr
CS Department of Surgery, Milton S. Hershey Medical Center, Pennsylvania State University, Hershey 17033.
NC DK-40069 (NIDDK)
HL-01502 (NHLBI)
SO American journal of physiology, (1990 Jun) 258 (6 Pt 2) F1546-53.
Journal code: 0370511. ISSN: 0002-9513.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199008
ED Entered STN: 19900907
Last Updated on STN: 20000303
Entered Medline: 19900802
AB The glutathione (GSH) content of rat kidney decreases after cessation of blood flow, falling to 40% of control levels 35 min after renal artery occlusion [R. C. Scaduto, Jr., V. H. Gattone II, L. W. Grotyohann, J. Wertz, and L. F. Martin. Am. J. Physiol. 255 (Renal Fluid Electrolyte Physiol. 24): F911-F921, 1988]. Renal GSH levels remained depressed for at least 2 h after resumption of blood flow. Because GSH functions in the removal of free radicals, and lipid peroxidation is a free radical-initiated process that occurs in the ischemic kidney, we investigated the fate of this GSH pool in the ischemic kidney. Using high-performance liquid chromatography to measure thiols, we found the loss of GSH to be associated with a stoichiometric accumulation of cysteine in the kidney. Moreover, preischemic labeling of the renal GSH pool with 35S led to accumulation of [35S]cysteine during ischemia that had the same specific activity as that of tissue GSH. Formation of cysteine during ischemia was suppressed in rats pretreated with acivicin, an inhibitor of gamma-glutamyltransferase (gamma-GT), although the degree of suppression was small in comparison to the extent of gamma-GT inhibition. During the initial 2 min of blood reflow after ischemia, tissue cysteine returned to control levels, and a transient increase in the cysteine content of renal venous blood was observed. After ischemia, renal GSH levels remained depressed, but postischemic GSH levels could be increased by administration of N-acetylcysteine during the ischemic period. (ABSTRACT TRUNCATED AT 250 WORDS)
CT Check Tags: Male
Acetylcysteine: PD, pharmacology
Animals
Antimetabolites: PD, pharmacology
Cysteine: ME, metabolism
*Glutathione: ME, metabolism
*Ischemia: ME, metabolism
Isoxazoles: PD, pharmacology
*Kidney: BS, blood supply
Kidney: ME, metabolism
Rats
Reperfusion
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
Sulfhydryl Compounds: ME, metabolism
gamma-Glutamyltransferase: AI, antagonists & inhibitors
RN 52-90-4 (Cysteine); 52583-41-2 (acivicin); 616-91-1

(Acetylcysteine); 70-18-8 (Glutathione)
CN 0 (Antimetabolites); 0 (Isoxazoles); 0 (Sulfhydryl Compounds); EC 2.3.2.2 (gamma-Glutamyltransferase)

L30 ANSWER 16 OF 16 MEDLINE on STN
AN 80146834 MEDLINE
DN PubMed ID: 6102405
TI The inhibition of gamma-glutamyl transpeptidase from human pancreatic carcinoma cells by (alpha S,5S)-alpha-amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid (AT-125; NSC-163501).
AU Allen L; Meck R; Yunis A
SO Research communications in chemical pathology and pharmacology, (1980 Jan) 27 (1) 175-82.
Journal code: 0244734. ISSN: 0034-5164.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198005
ED Entered STN: 19900315
Last Updated on STN: 19950206
Entered Medline: 19800514
AB AT-125, (alpha S, 5S)-alpha-amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid, at a concentration of 5 microM was found to inhibit the growth of human pancreatic carcinoma cells (MIA PaCa-2) by 78% after 72 hours in continuous culture. It was found that MIA PaCa-2 gamma-glutamyl transpeptidase (10 nmol/min/10(6) cells) was irreversibly inactivated by AT-125 with an inactivation half-life of 80 minutes at 450 microM.
CT *Antibiotics, Antineoplastic: PD, pharmacology
Cells, Cultured
*Glycine: AA, analogs & derivatives
Glycine: PD, pharmacology
Half-Life
Humans
*Isoxazoles: PD, pharmacology
*Oxazoles: PD, pharmacology
*Pancreatic Neoplasms: EN, enzymology
Research Support, U.S. Gov't, P.H.S.
Time Factors
*gamma-Glutamyltransferase: AI, antagonists & inhibitors
RN 52583-41-2 (acivicin); 56-40-6 (Glycine)
CN 0 (Antibiotics, Antineoplastic); 0 (Isoxazoles); 0 (Oxazoles); EC 2.3.2.2 (gamma-Glutamyltransferase)

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L40 ANSWER 1 OF 1 EMBASE
on STN
AN 2001288286 EMBASE
TI Enhanced gamma-glutamyl transpeptidase

expression and superoxide production in Mpv17(-/-) glomerulosclerosis mice.

AU **Wagner G.**; Stettmaier K.; Bors W.; **Sies H.**; Wagner E.-M.; Reuter A.; **Weiher H.**

CS G. Wagner, Inst. fur Physiol. Chemie I, Heinrich-Heine-Universitat, D-40001 Dusseldorf, Germany

SO Biological Chemistry, (2001) Vol. 382, No. 7, pp. 1019-1025.
Refs: 49
ISSN: 1431-6730 CODEN: BICHF3

CY Germany

DT Journal; Article

FS 028 Urology and Nephrology
029 Clinical Biochemistry

LA English

SL English

ED Entered STN: 20010830
Last Updated on STN: 20010830

AB Recently, γ **-glutamyl transpeptidase**, which initiates cleavage of extracellular glutathione, has been shown to promote oxidative damage to cells. Here we examined a murine disease model of glomerulosclerosis, involving loss of the Mpv17 gene coding for a peroxisomal protein. In Mpv17(-/-) cells, enzyme activity and mRNA expression (examined by quantitative RT-PCR) of membrane-bound . **gamma.-glutamyl transpeptidase** were increased, while plasma glutathione peroxidase and superoxide dismutase levels were lowered. Superoxide anion production in these cells was increased as documented by electron spin resonance spectroscopy. In the presence of Mn(III)tetrakis(4-benzoic acid)porphyrin, the activities of **.gamma .-glutamyl transpeptidase** and plasma glutathione peroxidase were unchanged, suggesting a relationship between enzyme expression and the amount of reactive oxygen species. Inhibition of . **gamma.-glutamyl transpeptidase** by **acivicin** reverted the lowered plasma glutathione peroxidase and superoxide dismutase activities, indicating reciprocal control of gene expression for these enzymes.

CT Medical Descriptors:
***glomerulosclerosis**
protein expression
protein degradation
oxidative stress
genetic code
peroxisome
enzyme activity
reverse transcription polymerase chain reaction
blood level
electron spin resonance
gene expression regulation
nonhuman
mouse
animal experiment
animal model
controlled study
animal cell
article
priority journal
Drug Descriptors:
***gamma glutamyltransferase: EC, endogenous compound**
*superoxide dismutase: EC, endogenous compound
glutathione peroxidase: EC, endogenous compound
cell protein: EC, endogenous compound
Mpv 17 protein: EC, endogenous compound
messenger RNA: EC, endogenous compound
porphyrin derivative
manganese(III)tetrakis(4 benzoic acid)porphyrin
reactive oxygen metabolite: EC, endogenous compound
acivicin

unclassified drug
RN (gamma **glutamyltransferase**) 85876-02-4; (superoxide dismutase) 37294-21-6, 9016-01-7, 9054-89-1; (glutathione peroxidase) 9013-66-5; (**acivicin**) **42228-92-2**

=> d all l43 tot

L43 ANSWER 1 OF 13 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN **2000416962** EMBASE
TI The species-dependent metabolism of Efavirenz produces a nephrotoxic glutathione conjugate in rats.
AU Mutlib A.E.; Gerson R.J.; Meunier P.C.; Haley P.J.; Chen H.; Gan L.S.; Davies M.H.; Gemzik B.; Christ D.D.; Krahn D.F.; Markwalder J.A.; Seitz S.P.; Robertson R.T.; Miwa G.T.
CS A.E. Mutlib, Drug Metabol./Pharmacokinetics Sec., DuPont Pharmaceuticals Company, Stine-Haskell Research Center, Elkton Road, Newark, DE 19714, United States
SO Toxicology and Applied Pharmacology, (15 Nov 2000) Vol. 169, No. 1, pp. 102-113.
Refs: 52
ISSN: 0041-008X CODEN: TXAPA
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
028 Urology and Nephrology
030 Pharmacology
037 Drug Literature Index
052 Toxicology
LA English
SL English
ED Entered STN: 20001221
Last Updated on STN: 20001221
AB Efavirenz, a potent nonnucleoside reverse transcriptase inhibitor widely prescribed for the treatment of HIV infection, produces renal tubular epithelial cell necrosis in rats but not in cynomolgus monkeys or humans. This species selectivity in nephrotoxicity could result from differences in the production or processing of reactive metabolites, or both. A detailed comparison of the metabolites produced by rats, monkeys, and humans revealed that rats produce a unique glutathione adduct. The mechanism of formation and role of this glutathione adduct in the renal toxicity were investigated using both chemical and biochemical probes. Efavirenz was labeled at the methine position on the cyclopropyl ring with the stable isotope deuterium, effectively reducing the formation of the cyclopropanol metabolite, an obligate precursor to the glutathione adduct. This substitution markedly reduced both the incidence and severity of nephrotoxicity as measured histologically. Further processing of this glutathione adduct was also important in producing the lesion and was demonstrated by inhibiting γ- **glutamyltranspeptidase** with **acivicin** pretreatment (10 mg/kg, IV) prior to dosing with efavirenz. Again, both the incidence and severity of the nephrotoxicity were reduced, such that four of nine rats given **acivicin** were without detectable lesions. These studies provide compelling evidence that a species-specific formation of glutathione conjugate(s) from efavirenz is involved in producing nephrotoxicity in rats. Mechanisms are proposed for the formation of reactive metabolites that could be responsible for the renal toxicity observed in rats. (C) 2000 Academic Press.
CT Medical Descriptors:
*glutathione metabolism
***nephrotoxicity: ET, etiology**
***kidney tubule necrosis: ET, etiology**
species difference
kidney tubule epithelium
histopathology

morbidity
disease severity
drug mechanism
drug structure
enzyme inhibition
drug urine level
drug effect
drug metabolism
nonhuman
male
rat
animal experiment
animal model
controlled study
animal tissue
article
Drug Descriptors:
*efavirenz: TO, drug toxicity
*efavirenz: PD, pharmacology
*RNA directed DNA polymerase inhibitor: TO, drug toxicity
*RNA directed DNA polymerase inhibitor: PD, pharmacology
***acivicin: PD, pharmacology**
*glutathione derivative: TO, drug toxicity
*glutathione derivative: EC, endogenous compound
cyclopropanecarboxylic acid derivative
deuterium
gamma glutamyltransferase: EC, endogenous compound
drug metabolite: TO, drug toxicity
glutathione: EC, endogenous compound

RN (efavirenz) 154598-52-4; (**acivicin**) **42228-92-2**; (deuterium) 7782-39-0; (gamma **glutamyltransferase**) 85876-02-4; (glutathione) 70-18-8

CO Du Pont

L43 ANSWER 2 OF 13 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

AN **2000234081** EMBASE

TI Contribution of γ **glutamyl transpeptidase** to oxidative damage of ischemic rat kidney.

AU Cutrin J.C.; Zingaro B.; Camandola S.; Boveris A.; Pompella A.; Poli G.

CS Dr. J.C. Cutrin, Universita di Torino, Dipto. di Sci. Cliniche e Biologiche, ASL San Luigi Gonzaga, Regione Gonzole 10, 10043 Orbassano, Torino, Italy. juan.cutrin@sluigi.unito.it

SO Kidney International, (2000) Vol. 57, No. 2, pp. 526-533.
Refs: 40
ISSN: 0085-2538 CODEN: KDYIA5

CY United States

DT Journal; Article

FS 005 General Pathology and Pathological Anatomy
028 Urology and Nephrology

LA English

SL English

ED Entered STN: 20000720
Last Updated on STN: 20000720

AB Background. A variety of mechanisms have been considered in the pathogenesis of the cell damage occurring in the kidney that is undergoing transient ischemia. However, little information is available about the role of oxidative stress in building up the tissue injury in the hypoxic organ during short-term ischemia. Methods. After a standard brief period (25 min) of unilateral kidney ischemia in rats, pretreated or not with **acivicin** (60 μmol/L/kg i.v.), tissue samples from both ischemic and not ischemic kidneys were obtained to measure malondialdehyde (MDA) and glutathione (GSH) content, γ **glutamyl transpeptidase** (**GGT**) activity by spectrophotometry, localization and intensity of enzyme activity, and tissue damage by histochemistry. Results. **GGT** activity was found to be

increased in both cortical and medullar zones of the ischemic kidneys, where the GSH level was only slightly decreased and the MDA level, in contrast, was markedly increased; in parallel, the cytosolic volume of the proximal tubular (PT) cells showed a significant increment. The animal pretreatment with **acivicin**, a specific inhibitor of **GGT**, besides preventing the up-regulation of the enzyme during ischemia, afforded good protection against the observed changes of MDA and GSH tissue levels, as well as of tubular cell volume. Conclusions. Ex vivo data supporting a net pro-oxidant effect of up-regulated **GGT** during short- term ischemia of rat kidney have been obtained. The enzyme stimulation appears to contribute to the renal morphological damage exerted by a brief hypoxic condition at the level of PT cells. The actual impact on kidney function by **GGT**-dependent oxidative damage during transient ischemia and the potential protective action of **GGT** inhibitors require subsequent investigation.

CT Medical Descriptors:
***kidney ischemia**
enzyme activity
enzyme localization
histochemistry
spectrophotometry
nonhuman
male
rat
animal experiment
animal model
controlled study
animal tissue
article
priority journal
Drug Descriptors:
***gamma glutamyltransferase: EC, endogenous compound**
acivicin
malonaldehyde: EC, endogenous compound
glutathione peroxidase: EC, endogenous compound

RN (gamma **glutamyltransferase**) 85876-02-4; (**acivicin**) **42228-92-2**; (malonaldehyde) 542-78-9; (glutathione peroxidase) 9013-66-5

L43 ANSWER 3 OF 13 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

AN **1999298306** EMBASE

TI Glutathione-dependent metabolism of cis-3-(9H-purin-6-ylthio)acrylic acid to yield the chemotherapeutic drug 6-mercaptopurine: Evidence for two distinct mechanisms in rats.

AU Gunnarsdottir S.; Elfarra A.A.

CS A.A. Elfarra, Dept. of Comparative Biosciences, University of Wisconsin, School of Veterinary Medicine, 2015 Linden Dr., Madison, WI 53706, United States. elfarraa@svm.vetmed.wisc.edu

SO Journal of Pharmacology and Experimental Therapeutics, (1999) Vol. 290, No. 3, pp. 950-957.
Refs: 39
ISSN: 0022-3565 CODEN: JPETAB

CY United States

DT Journal; Article

FS 030 Pharmacology
037 Drug Literature Index

LA English

SL English

ED Entered STN: 19990910
Last Updated on STN: 19990910

AB cis-3-(9H-Purin-6-ylthio)acrylic acid (PTA) is a structural analog of azathioprine, a prodrug of the antitumor and immunosuppressive drug 6-mercaptopurine (6-MP). In this study, we examined the in vitro and in vivo metabolism of PTA in rats. Two metabolites of PTA, 6-MP and the major metabolite, S-(9H-purin-6-yl)glutathione (PG), were formed in a

time- and GSH-dependent manner in vitro. Formation of 6-MP and PG occurred nonenzymatically, but 6-MP formation was enhanced 2-and 7-fold by the addition of liver and kidney homogenates, respectively. Purified rat liver glutathione S-transferases enhanced 6-MP formation from PTA by 1.8-fold, whereas human recombinant α, μ, and π isozymes enhanced 6-MP formation by 1.7-, 1.3-, and 1.3-fold, respectively. In kidney homogenate incubations, PG accumulation was only observed during the first 15 min because of further metabolism by γ - **glutamyl-transpeptidase**, **dipeptidase**, and β-lyase to yield 6-MP, as indicated by the use of the inhibitors **acivicin** and aminooxy-acetic acid. Based on these results and other lines of evidence, two different GSH- dependent pathways are proposed for 6-MP formation: an indirect pathway involving PG formation and further metabolism to 6-MP, and a direct pathway in which PTA acts as a Michael acceptor. HPLC analyses of urine of rats treated i.p. with PTA (100 mg/kg) showed that 6-MP was formed in vivo and excreted in urine without apparent liver or kidney toxicity. Collectively, these studies show that PTA is metabolized to 6-MP both in vitro and in vivo and may therefore be a useful prodrug of 6-MP.

CT Medical Descriptors:
*glutathione metabolism
*cancer chemotherapy
drug mechanism
antineoplastic activity
immunosuppressive treatment
drug metabolism
enzyme subunit
liver homogenate
nephrotoxicity
structure analysis
human
nonhuman
rat
animal model
human cell
animal cell
article
priority journal
Drug Descriptors:
*glutathione: EC, endogenous compound
*azathioprine derivative: PD, pharmacology
*3 (9h purin 6 ylthio)acrylic acid: PD, pharmacology
*mercaptopurine: PD, pharmacology
gamma glutamyltransferase: EC, endogenous compound
dipeptidase: EC, endogenous compound
acivicin: PD, pharmacology
aminooxyacetic acid: PD, pharmacology

RN (glutathione) 70-18-8; (mercaptopurine) 31441-78-8, 50-44-2, 6112-76-1; (gamma **glutamyltransferase**) 85876-02-4; (dipeptidase) 9031-99-6; (**acivicin**) **42228-92-2**; (aminooxyacetic acid) 2921-14-4, 645-88-5

CO Sigma (United States)

L43 ANSWER 4 OF 13 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

AN **1999027532** EMBASE

TI Synthesis of the antioxidant glutathione in neurons: Supply by astrocytes of CysGly as precursor for neuronal glutathione.

AU Dringen R.; Pfeiffer B.; Hamprecht B.

CS Dr. R. Dringen, Phys.-Chemisches Inst. der Univ., Hoppe-Seyler-Strasse 4, D-72076 Tubingen, Germany

SO Journal of Neuroscience, (15 Jan 1999) Vol. 19, No. 2, pp. 562-569.
Refs: 49
ISSN: 0270-6474 CODEN: JNRSDS

CY United States

DT Journal; Article

FS 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
029 Clinical Biochemistry
LA English
SL English
ED Entered STN: 19990218
Last Updated on STN: 19990218
AB Deficiency of the antioxidant glutathione in brain appears to be connected with several diseases characterized by neuronal loss. To study neuronal glutathione metabolism and metabolic interactions between neurons and astrocytes in this respect, neuron-rich primary cultures and transient cocultures of neurons and astroglial cells were used. Coincubation of neurons with astroglial cells resulted within 24 hr of incubation in a neuronal glutathione content twice that of neurons incubated in the absence of astroglial cells. In cultured neurons, the availability of cysteine limited the cellular level of glutathione. During a 4 hr incubation in a minimal medium lacking all amino acids except cysteine, the amount of neuronal glutathione was doubled. Besides cysteine, also the dipeptides CysGly and γGluCys were able to serve as glutathione precursors and caused a concentration-dependent increase in glutathione content. Concentrations giving half-maximal effects were 5, 5, and 200 μM for cysteine, CysGly, and γGluCys, respectively. In the transient cocultures, the astroglia-mediated increase in neuronal glutathione was suppressed by **acivicin**, an inhibitor of the astroglial ectoenzyme γ **-glutamyl transpeptidase**, which generates CysGly from glutathione. These data suggest the following metabolic interaction in glutathione metabolism of brain cells: the ectoenzyme γ **-glutamyl transpeptidase** uses as substrate the glutathione released by astrocytes to generate the dipeptide CysGly that is subsequently used by neurons as precursor for glutathione synthesis.
CT Medical Descriptors:
*astrocyte
*glutathione metabolism
*oxidative stress
***nerve degeneration: ET, etiology**
nerve cell
macroglia
coculture
biosynthesis
antioxidant activity
cell viability
cell lysate
nonhuman
rat
controlled study
animal cell
embryo
article
priority journal
Drug Descriptors:
*glutathione: EC, endogenous compound
*antioxidant: EC, endogenous compound
*cysteinylglycine
*dipeptide
gamma glutamyltransferase: EC, endogenous compound
cysteine
acivicin
RN (glutathione) 70-18-8; (gamma **glutamyltransferase**) 85876-02-4; (cysteine) 4371-52-2, 52-89-1, 52-90-4; (**acivicin**) **42228-92-2**

L43 ANSWER 5 OF 13 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN **96356214** EMBASE
DN 1996356214

TI Cisplatin nephrotoxicity: Inhibition of γ -glutamyl **transpeptidase** blocks the nephrotoxicity of cisplatin without reducing platinum concentrations in the kidney.

AU Hanigan M.H.; Gallagher B.C.; Taylor P.T. Jr.; Grover L.; Eddy G.L.
CS School of Medicine, University of Virginia, Box 439,Charlottesville, VA 22908, United States

SO American Journal of Obstetrics and Gynecology, (1996) Vol. 175, No. 2, pp. 270-274.
ISSN: 0002-9378 CODEN: AJOGAH
CY United States
DT Journal; Conference Article
FS 016 Cancer
028 Urology and Nephrology
030 Pharmacology
037 Drug Literature Index
LA English
SL English
ED Entered STN: 961218
Last Updated on STN: 961218

AB OBJECTIVE: Inhibition of γ -**glutamyl transpeptidase** activity by **acivicin** or a large bolus of intravenous glutathione blocks the nephrotoxicity of cisplatin. The purpose of this study was to determine whether these compounds inhibit nephrotoxicity by reducing the amount of platinum retained by the kidney. STUDY DESIGN: The platinum concentration in urine and kidney of cisplatin-treated rats was determined by graphite furnace atomic absorption spectroscopy. Tissues from three experimental groups of rats were analyzed. The first group was treated with a nephrotoxic dose of cisplatin. The second group was treated with **acivicin** before cisplatin. The third group received a bolus of glutathione before cisplatin. Urine collected for 3 hours after the injection of cisplatin and kidney tissue from animals 5 days after treatment were analyzed for platinum content. RESULTS: Urine from animals pretreated with **acivicin** had the same concentration of platinum as that of control animals treated with cisplatin alone. Analysis of kidney tissue, blood urea nitrogen and serum creatinine 5 days after treatment showed that pretreatment with **acivicin** or glutathione blocked the nephrotoxicity of cisplatin. However, these agents did not alter the concentration of platinum in the kidney. CONCLUSIONS: The data in this study reveal that pretreatment with **acivicin** or glutathione does not block the uptake of platinum into the kidney nor do these agents reduce the concentration of platinum retained by the kidney. The mechanism by which these agents may inhibit the nephrotoxicity of cisplatin is discussed.

CT Medical Descriptors:
***nephrotoxicity: PC, prevention**
animal experiment
animal tissue
atomic absorption spectrometry
conference paper
controlled study
creatinine blood level
drug tissue level
drug uptake
drug urine level
enzyme inhibition
human
intravenous drug administration
kidney
male
priority journal
rat
urea nitrogen blood level
Drug Descriptors:
***acivicin: DO, drug dose**
***acivicin: PD, pharmacology**

*cisplatin: DO, drug dose
*cisplatin: TO, drug toxicity
*cisplatin: PD, pharmacology
***gamma glutamyltransferase: EC, endogenous compound**
*glutathione: AD, drug administration
*glutathione: DO, drug dose
*glutathione: PD, pharmacology
*platinum: CR, drug concentration
creatinine: EC, endogenous compound
RN (**acivicin**) **42228-92-2**; (cisplatin) 15663-27-1, 26035-31-4, 96081-74-2; (gamma **glutamyltransferase**) 85876-02-4; (glutathione) 70-18-8; (platinum) 7440-06-4; (creatinine) 19230-81-0, 60-27-5

L43 ANSWER 6 OF 13 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN **94362282** EMBASE
DN 1994362282
TI Inhibition of γ -**glutamyl transpeptidase** activity by **acivicin** in vivo protects the kidney from cisplatin-induced toxicity.
AU Hanigan M.H.; Gallagher B.C.; Taylor Jr. P.T.; Large M.K.
CS Department of Cell Biology, School of Medicine, University of Virginia,Charlottesville, VA 22908, United States
SO Cancer Research, (1994) Vol. 54, No. 22, pp. 5925-5929. ISSN: 0008-5472 CODEN: CNREA8
CY United States
DT Journal; Article
FS 016 Cancer
028 Urology and Nephrology
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LA English
SL English
ED Entered STN: 950112
Last Updated on STN: 950112
AB Cisplatin [cis-dichlorodiammineplatinum(II)] is a widely used chemotherapeutic drug that is toxic to the proximal tubule cells of the kidney. γ -**Glutamyl transpeptidase** (**GGT**) is localized to the luminal surface of the renal proximal tubules. **GGT** catalyzes the initial step in the metabolism of glutathione-conjugated drugs to mercapturic acids, some of which are severely nephrotoxic. We proposed that the nephrotoxicity of cisplatin was dependent on the cleavage of a cisplatin-glutathione conjugate by **GGT**. To test this hypothesis, renal **GGT** activity was blocked in male Sprague-Dawley rats by **acivicin**, a non-competitive inhibitor of **GGT**. Treatment with cisplatin alone caused extensive acute necrosis of the proximal tubules, but the proximal tubule cells appeared normal in rats treated with **acivicin** prior to cisplatin. Blood urea nitrogen and serum creatinine levels confirmed the protective effect of **acivicin**. Glutathione is a physiological substrate for **GGT**. Administration of an 83-fold excess of glutathione 30 min prior to cisplatin also inhibited cisplatin-induced nephrotoxicity. These data provide important new evidence that a large bolus of glutathione blocks the nephrotoxicity of cisplatin by competitively inhibiting **GGT**. These results indicate that cisplatin is conjugated to glutathione in vivo. The platinum-glutathione conjugate is nontoxic until metabolized by the proximal tubule cells. Formation of the nephrotoxic derivative of cisplatin requires **GGT** activity.
CT Medical Descriptors:
***acute kidney tubule necrosis: ET, etiology**
*kidney proximal tubule
animal model
animal tissue

article
body weight
controlled study
drug conjugation
drug metabolism
enzyme activity
enzyme inhibition
intravenous drug administration
nonhuman
priority journal
protection
rat
Drug Descriptors:
***acivicin: AD, drug administration**
***acivicin: CB, drug combination**
***acivicin: DO, drug dose**
***acivicin: IT, drug interaction**
***acivicin: PD, pharmacology**
*cisplatin: TO, drug toxicity
*cisplatin: DO, drug dose
*cisplatin: IT, drug interaction
*cisplatin: CB, drug combination
***gamma glutamyltransferase: EC, endogenous compound**
acetylcysteine
creatinine: EC, endogenous compound
glutathione
nitrogen: EC, endogenous compound
urea: EC, endogenous compound
RN (**acivicin**) **42228-92-2**; (cisplatin) 15663-27-1, 26035-31-4, 96081-74-2; (gamma **glutamyltransferase**) 85876-02-4; (acetylcysteine) 616-91-1; (creatinine) 19230-81-0, 60-27-5; (glutathione) 70-18-8; (nitrogen) 7727-37-9; (urea) 57-13-6
CN (1) **At 125**; (2) Platinol
CO (1) Sigma (United States); (2) Bristol (United States)

L43 ANSWER 7 OF 13 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN **93009711** EMBASE
DN 1993009711
TI The effects of 2,3,5-(triglutathion-S-yl)hydroquinone on renal mitochondrial respiratory function in vivo and in vitro: Possible role in cytotoxicity.
AU Hill B.A.; Monks T.J.; Lau S.S.
CS Division of Pharmacology/Toxicology, College of Pharmacy, University of Texas,Austin, TX 78712, United States
SO Toxicology and Applied Pharmacology, (1992) Vol. 117, No. 2, pp. 165-171. ISSN: 0041-008X CODEN: TXAPA
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
028 Urology and Nephrology
029 Clinical Biochemistry
052 Toxicology
037 Drug Literature Index
LA English
SL English
ED Entered STN: 930207
Last Updated on STN: 930207
AB Administration of 2,3,5-(triglutathion-S-yl)hydroquinone [2,3,5-(triGSyl)HQ] to rats causes severe renal proximal tubular necrosis. Although the cellular target(s) for 2,3,5-(triGSyl)HQ is not known, substantial evidence implicates mitochondria as the primary cellular target for aliphatic S-conjugates. To determine whether mitochondria are targets for 2,3,5-(triGSyl)HQ, the in vivo and in vitro effects of this conjugate on rat renal mitochondria (RRM) were investigated. In vitro exposure of RRM to 2,3,5-(triGSyl)HQ inhibited site I-supported

respiration to a much greater extent than site II-supported respiration. Inhibition of mitochondrial function, as manifested by decreases in the respiratory control ratios, were a consequence of significant elevations in state 4 respiration. Inhibition of constitutive γ -GT activity with **AT-125** had no effect on the ability of 2,3,5-(triGSyl)HQ to decrease mitochondrial function. The effects of 2,3,5-(triGSyl)HQ on mitochondrial function in vivo were subsequently assessed. Shortly (0.5-2.0 hr) following administration of 2,3,5-(triGSyl)HQ (20 μmol/kg, iv) to rats, a significant elevation of state 4 respiration was observed. Thereafter (4-16 hr) state 4 respiration returned to control values and state 3 respiration became significantly depressed. A total collapse in RRM function occurred by 24 hr. The effects of 2,3,5-(triGSyl)HQ on state 4 respiration preceded significant elevations in blood urea nitrogen, which occurred at 8 hr. However, pretreatment of animals with probenecid, an inhibitor of organic anion transport, caused a significant decrease in the 2,3,5-(triGSyl)HQ-mediated elevations in state 4 respiration at 1 hr, without preventing the subsequent development of renal necrosis. In contrast, **AT-125**, which protected animals from 2,3,5-(triGSyl)HQ-mediated nephrotoxicity, had no effect on the early (1 hr) elevations in state 4 respiration but did prevent the later (8 hr) decreases in state 3 respiration. The data suggest that the early elevation in state 4 respiration observed in vivo is unlikely to contribute to 2,3,5-(triGSyl)HQ-mediated nephrotoxicity. The relationship between the decrease in state 3 respiration seen at later time points and the subsequent development of toxicity require further study before a cause and effect relationship can be determined.

CT Medical Descriptors:
*cytotoxicity
***kidney tubule necrosis**
*mitochondrial respiration
animal experiment
animal tissue
article
concentration response
controlled study
intraperitoneal drug administration
male
nonhuman
priority journal
rat
urea nitrogen blood level
Drug Descriptors:
2,3,5 tris(glutathion s yl)hydroquinone: TO, drug toxicity
acivicin: PD, pharmacology
gamma glutamyltransferase: EC, endogenous compound
hydroquinone: TO, drug toxicity
probenecid: PD, pharmacology
urea: EC, endogenous compound
unclassified drug

RN **(acivicin) 42228-92-2**; (gamma **glutamyltransferase**) 85876-02-4; (hydroquinone) 123-31-9; (probenecid) 57-66-9; (urea) 57-13-6

CN **(1) At 125**

CO (1) National cancer institute

L43 ANSWER 8 OF 13 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

AN **91267891** EMBASE

DN 1991267891

TI Inhibition of γ **-glutamyl transpeptidase** potentiates the nephrotoxicity of glutathione-conjugated chlorohydroquinones.

AU Mertens J.J.W.M.; Temmink J.H.M.; Van Bladeren P.J.; Jones T.W.; Lo H.-H.; Lau S.S.; Monks T.J.

CS Division of Pharmacology and Toxicology, College of Pharmacy, University

of Texas, Austin, TX 78712, United States
SO Toxicology and Applied Pharmacology, (1991) Vol. 110, No. 1, pp. 45-60.
ISSN: 0041-008X CODEN: TXAPA
CY United States
DT Journal; Article
FS 028 Urology and Nephrology
029 Clinical Biochemistry
035 Occupational Health and Industrial Medicine
052 Toxicology
037 Drug Literature Index
LA English
SL English
ED Entered STN: 911216
Last Updated on STN: 911216
AB Administration of either 2,5-dichloro-3-(glutathion-S-yl)-1,4-benzoquinone (DC-[GSyl]BQ) or 2,5,6-trichloro-3-(glutathion-S-yl)-1,4-benzoquinone (TC-[GSyl]BQ) to male Sprague-Dawley rats caused dose-dependent (50-200 μmol/kg; iv) renal proximal tubular necrosis, as evidenced by elevations in blood urea nitrogen (BUN), and in the urinary excretion of lactate dehydrogenase (LDH), γ -glutamyl **transpeptidase** (γ -GT) and glucose.
Renal proximal tubular necrosis was also confirmed by histological examination of kidney slices prepared from DC-(GSyl)BQ- and TC-(GSyl)BQ-treated animals. Administration of the corresponding hydroquinone conjugates (DC-[GSyl]HQ and TC-[GSyl]HQ), prepared by reducing the quinones with a threefold molar excess of ascorbic acid, resulted in a substantial increase in nephrotoxicity. Moreover, in contrast to other glutathione (GSH)-conjugated hydroquinones, the nephrotoxicity of both DC-(GSyl)HQ and TC-(GSyl)HQ was potentiated when rats were pretreated with **AT-125**, an irreversible inhibitor of γ -GT. Neither the quinone-GSH nor the hydroquinone-GSH conjugates caused any effect on liver histology or serum glutamate-pyruvate transaminase levels. The results suggest that coadministration of ascorbic acid with DC-(GSyl)BQ or TC-(GSyl)BQ decreases their interactions with extrarenal nucleophiles, including plasma proteins, and thus increases the concentration of the conjugates delivered to the kidney, and hence toxicity. Furthermore the ability of **AT-125** to potentiate the nephrotoxicity of DC-(GSyl)HQ and TC-(GSyl)HQ suggests that metabolism of these conjugates by . **gamma.-GT** constitutes a detoxication reaction.
CT Medical Descriptors:
*enzyme inhibition
***kidney tubule necrosis**
***nephrotoxicity**
animal experiment
animal tissue
article
male
nonhuman
priority journal
rat
Drug Descriptors:
*benzoquinone: TO, drug toxicity
***gamma glutamyltransferase: EC, endogenous compound**
*lactate dehydrogenase: EC, endogenous compound
acivicin: PD, pharmacology
ascorbic acid: PD, pharmacology
glucose: EC, endogenous compound
lactic acid: EC, endogenous compound
RN (gamma **glutamyltransferase**) 85876-02-4; (lactate dehydrogenase) 9001-60-9; (**acivicin**) **42228-92-2**; (ascorbic acid) 134-03-2, 15421-15-5, 50-81-7; (glucose) 50-99-7, 84778-64-3; (lactic acid) 113-21-3, 50-21-5
CN **At 125**

L43 ANSWER 9 OF 13 EMBASE

on STN
AN 90116335 EMBASE
DN 1990116335
TI The in vivo disposition of 2-bromo-[14C]hydroquinone and the effect of . **gamma.-glutamyl transpeptidase** inhibition.
AU Lau S.S.; Monks T.J.
CS Division of Pharmacology and Toxicology, College of Pharmacy, University of Texas, Austin, TX 78712, United States
SO Toxicology and Applied Pharmacology, (1990) Vol. 103, No. 1, pp. 121-132. ISSN: 0041-008X CODEN: TXAPA
CY United States
DT Journal; Article
FS 028 Urology and Nephrology
029 Clinical Biochemistry
035 Occupational Health and Industrial Medicine
052 Toxicology
037 Drug Literature Index
LA English
SL English
ED Entered STN: 911213
Last Updated on STN: 911213
AB We have previously shown that the renal necrosis observed after 2-bromohydroquinone (2-BrHQ) administration to rats is probably caused by the formation of 2-Br-(diglutathion-S-yl)HQ (2-Br-[diGSyl]HQ), since injection of this conjugate caused severe proximal tubular necrosis. In the present study we report the in vivo metabolism and covalent binding of 2-[14C]-BrHQ in male Sprague-Dawley rats. The major urinary and biliary metabolite was a glucuronide conjugate. In addition, 2-Br-(di-GSyl)HQ, 2-Br-3-(GSyl)HQ, 2-Br-5-(GSyl)HQ, and 2-Br-6-(GSyl)HQ were all detected as urinary and biliary metabolites of 2-BrHQ. The in vivo covalent binding of 2-[14C]BrHQ to kidney, pancreas, seminal vesicles, intestine, bone marrow, and liver was 21.8, 1.5, 1.2, 4.4, 1.8, and 2.6 nmol/mg protein, respectively. γ -**Glutamyl transpeptidase** (γ -**GT**) activity measured in these tissues was 947, 159, 55, 31, and 5.5 U/mg. Liver γ -**GT** activity was negligible (0.07 U/mg). Thus, maximum covalent binding and . **gamma.-GT** activity occurred in the kidney. Renal covalent binding and γ -**GT** activity were positively correlated with nephrotoxicity. Pretreatment of rats with L(αS,5S)-α-amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid (**AT-125**) inhibited renal γ -**GT**, after 24 hr, by 76%, renal covalent binding by 73%, and 2-BrHQ-mediated nephrotoxicity, as assessed by elevations in blood urea nitrogen (BUN), by 70%. These alterations were accompanied by an increase in the urinary excretion of each of the GSH conjugates, an increase in the fecal excretion of total radioactivity, and a decrease in plasma radioactivity at 24 hr. The present data provide evidence that 2-BrHQ is metabolized in vivo to nephrotoxic GSH conjugates. In addition, **AT-125** probably inhibits nephrotoxicity by decreasing the γ -**GT**-mediated renal proximal tubule accumulation of the toxic metabolites, thereby facilitating their excretion into urine. Although **AT-125** inhibited extrarenal γ -**GT** activity by 34-77%, it had variable effects on extrarenal covalent binding. Whereas covalent binding to renal tissue is probably mediated by reactive metabolites of the isomeric 2-Br-(GSyl)HQ conjugates, binding to extrarenal tissue may be mediated by both the conjugates and by 2-bromohydroquinone per se.
CT Medical Descriptors:
*bromohydroquinone
***nephrotoxicity**
covalent bond
enzyme inhibition
rat
toxicokinetics
xenobiotic metabolism
animal experiment

nonhuman
male
article
priority journal
Drug Descriptors:
*gamma glutamyltransferase
radioisotope
*acivicin
RN (gamma glutamyltransferase) 85876-02-4; (acivicin) 42228-92-2
CN (1) At 125
CO (1) National cancer institute

L43 ANSWER 10 OF 13 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 90100113 EMBASE
DN 1990100113
TI Role of γ- glutamyltranspeptidase in renal uptake and toxicity of inorganic mercury in mice.
AU Tanaka T.; Naganuma A.; Imura N.
CS Department of Public Health, School Pharmaceutical Science, Kitasato University, 9-1 Shirokane 5-chome,Minato-ku, Tokyo 108, Japan
SO Toxicology, (1990) Vol. 60, No. 3, pp. 187-198.
ISSN: 0300-483X CODEN: TXCYAC
CY Ireland
DT Journal; Article
FS 028 Urology and Nephrology
029 Clinical Biochemistry
052 Toxicology
LA English
SL English
ED Entered STN: 911213
Last Updated on STN: 911213
AB The role of renal glutathione (GSH) metabolism as a mediating factor in the renal uptake and toxicity of inorganic mercury was investigated in mice by preadministering a γ- glutamyltranspeptidase (GGT) inhibitor, acivicin. Pretreatment with acivicin (0.25, 1.0 or 2.5 mmol/kg, i.p.) led to a dose-dependent decrease in renal mercury content and increases in mercury and GSH contents in urine measured 2 h after HgCl2 injection (18 μmol/kg, i.v.). Acivicin pretreatment also ameliorated the renal and lethal toxicity caused by administration of inorganic mercury. Treatment of the mice with 1,2-dichloro-4-nitrobenzene (DCNB, 2.5 mmol/kg, i.p.), a specific depletor of hepatic GSH, prior to HgCl2 injection substantially reduced renal Hg content and consequently reduced the renal damage. In addition, coadministration of GSH (36 μmol/kg, i.v.) with HgCl2 increased the renal Hg content measured 5 min after HgCl2 injection to 2.6 fold higher than that of mice treated with HgCl2 alone. These results suggest that renal uptake of inorganic mercury, which is supposedly transported to the kidney as a mercury-GSH complex, is dependent on a reaction catalyzed by GGT on the outer surface of the renal brush border membrane in the same manner as the metabolism of GSH.
CT Medical Descriptors:
*nephrotoxicity
bioaccumulation
kidney
mouse
animal experiment
nonhuman
male
article
priority journal
Drug Descriptors:
*gamma glutamyltransferase
*glutathione
*mercury

1,2 dichloro 4 nitrobenzene
acivicin
RN (gamma **glutamyltransferase**) 85876-02-4; (glutathione) 70-18-8; (mercury) 14302-87-5, 7439-97-6; (1,2 dichloro 4 nitrobenzene) 99-54-7; (**acivicin**) **42228-92-2**

L43 ANSWER 11 OF 13 EMBASE
on STN
AN **90040167** EMBASE
DN 1990040167
TI Role of γ- **glutamyltranspeptidase** and β-lyase in the nephrotoxicity of hexachloro-1,3-butadiene and methyl mercury in mice.
AU De Ceaurriz J.; Ban M.
CS INRS, Avenue de Bourgogne,54501 Vandoeuvre, France
SO Toxicology Letters, (1990) Vol. 50, No. 2-3, pp. 249-256.
ISSN: 0378-4274 CODEN: TOLED5
CY Netherlands
DT Journal; Article
FS 037 Drug Literature Index
028 Urology and Nephrology
029 Clinical Biochemistry
046 Environmental Health and Pollution Control
052 Toxicology
LA English
SL English
ED Entered STN: 911213
Last Updated on STN: 911213
AB Male Swiss OF1 mice recieved a single oral dose of either 80 mg/kg hexachloro-1,3-butadiene (HCBD) or 80 mg/kg methyl mercury (MeHg). Examination of cryostat kidney sections stained for alkaline phosphatase (APP) revealed damage to about 50% of the proximal tubules after 8 h. Pretreatment with the γ- **glutamyltranspeptidase** (. **gamma.-GT**) inactivator **AT-125** (**Acivin**, 50 mg/kg i.p., plus 50 mg/kg p.o.), reduced the number of damaged tubules by 59 and 58% in mice treated with HCBD and MeHg, respectively. Pretreatment with the two β-lyase inhibitors, amino-oxyacetic acid (AOAA, 3 x 100 mg/kg p.o.) and DL-proparagylglycine (PPG, 300 mg/kg i.p. plus 300 mg/kg p.o.), reduced HCBD nephrotoxicity by 46 and 59%, respectively, but did not protect against MeHg nephrotoxicity. The results support a role for γ -**GT** and β-lyase in the mouse renal toxicity of HCBD and implicate . **gamma.-GT** but not β-lyase in MeHg-induced nephrotoxicity in mice.
CT Medical Descriptors:
*beta lyase
***nephrotoxicity**
kidney proximal tubule
mouse
animal experiment
nonhuman
male
intraperitoneal drug administration
oral drug administration
article
priority journal
Drug Descriptors:
***gamma glutamyltransferase**
*hexachlorobutadiene
*methylmercury
***acivicin**
*aminooxyacetic acid
*propargylglycine
RN (gamma **glutamyltransferase**) 85876-02-4; (hexachlorobutadiene) 87-68-3; (methylmercury) 16056-34-1, 593-74-8; (**acivicin**) **42228-92-2**; (aminooxyacetic acid) 2921-14-4, 645-88-5; (propargylglycine) 58160-95-5

CN (1) At 125
CO (1) Upjohn; Sigma

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AN **88210892** EMBASE
DN 1988210892
TI Effects of **AT-125** on the nephrotoxicity of hexachloro-1,3-butadiene in rats.
AU Davis M.E.
CS Department of Pharmacology and Toxicology, Health Science Center, West Virginia University, Morgantown, WV 26506, United States
SO Toxicology and Applied Pharmacology, (1988) Vol. 95, No. 1, pp. 44-52.
ISSN: 0041-008X CODEN: TXAPA
CY United States
DT Journal
FS 028 Urology and Nephrology
029 Clinical Biochemistry
052 Toxicology
030 Pharmacology
037 Drug Literature Index
LA English
SL English
ED Entered STN: 911211
Last Updated on STN: 911211
AB The role of γ -**glutamyl transpeptidase** (γ -**GTP**) in the nephrotoxicity of hexachloro-1,3-butadiene (HCBD) was studied using male Sprague-Dawley rats pretreated with **AT-125** (**Acivicin**; L-(αS, 5S)-α-amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid). Inhibition of γ -**GTP** by more than 95% did not affect urine output, glomerular filtration rate, or tubular reabsorption of filtrate, sodium, or glucose. Nephrotoxicity observed during the first 24 hr after HCBD was not decreased by inhibition of . **gamma.-GTP** and beyond 24 hr nephrotoxicity was increased, rather than decreased, in the **AT-125** -pretreated group. HCBD impairs glucose reabsorption and this was greatly increased in the **AT-125**-pretreated group, indicating that function of the initial segment of the nephron is impaired by HCBD. Since inhibition of γ -**GTP** did not protect against HCBD nephrotoxicity, it is concluded that γ -**GTP** inhibition does not limit the formation of metabolite(s) which cause HCBD nephrotoxicity. Therefore, distribution of γ-**glutamyltranspeptidase** does not account for the selective nephrotoxicity of hexachloro-1,3-butadiene.
CT Medical Descriptors:
***nephrotoxicity**
enzyme inhibition
rat
priority journal
animal experiment
nonhuman
intraperitoneal drug administration
Drug Descriptors:
***gamma glutamyltransferase**
*hexachlorobutadiene
***acivicin: DT, drug therapy**
RN (gamma **glutamyltransferase**) 85876-02-4; (hexachlorobutadiene) 87-68-3; (**acivicin**) **42228-92-2**
CN (1) At 125
CO (1) National cancer institute

L43 ANSWER 13 OF 13 EMBASE COPYRIGHT 2005 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN **87211012** EMBASE
DN 1987211012

TI Nephrotoxicity of S-(2-chloroethyl)glutathione in the Fischer rat: Evidence for γ- **glutamyltranspeptidase**-independent uptake by the kidney.

AU Kramer R.A.; Foureman G.; Greene K.E.; Reed D.J.
CS Laboratory of Experimental Therapeutics and Metabolism, Developmental Therapeutics Program, National Cancer Institute, Bethesda, MD, United States

SO Journal of Pharmacology and Experimental Therapeutics, (1987) Vol. 242, No. 2, pp. 741-748.
ISSN: 0022-3565 CODEN: JPETAB
CY United States
DT Journal
FS 028 Urology and Nephrology
052 Toxicology
030 Pharmacology
037 Drug Literature Index
LA English

AB S-(2-chloroethyl)glutathione (CEG; 270 μmol/kg) produced renal lesions that were confined to the proximal tubules of the outer stripe of the outer medulla and were similar to those lesions produced by the cysteine analog S-(2-chloroethyl)cysteine or by the nephrotoxic glutathione (GSH) adduct of 2-bromohydroquinone. These histopathologic changes in the kidney were correlated with alterations in renal function as reflected by dose- and time-dependent elevations in blood urea nitrogen levels as well as by the increased urinary excretion of protein, glucose and lactate dehydrogenase activity. The role of renal GSH metabolism as a mediating factor in the nephrotoxicity of these GSH conjugates was investigated by administering the γ- **glutamyltranspeptidase** inhibitor **AT-125** [L-(α-S,5S)-α-amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid]. Treatment with **AT-125** led to a dose-dependent decrease in renal γ-**glutamyltranspeptidase** activity that correlated inversely with increased GSH concentrations in the urine and kidney. Pretreatment with **AT-125** ameliorated 2-bromohydroquinone-induced renal toxicity but did not protect against the CEG-induced renal lesion. In fact, pretreatment with **AT-125** produced a dose-dependent potentiation of CEG renal toxicity. The CEG-induced renal lesion was dependent on a probenecid-sensitive transport system that was not involved in the toxicity of 2-bromohydroquinone. These studies demonstrate that CEG need not be metabolized by γ-**glutamyltranspeptidase** to the corresponding cysteine adduct [S-(2-chloroethyl)cysteine] in order to enter renal tubule cells and ultimately exert its nephrotoxic action.

CT Medical Descriptors:
*drug metabolism
***nephrotoxicity**
rat
intoxication
kidney
pharmacokinetics
therapy
intraperitoneal drug administration
drug response
histology
nonhuman
animal experiment
animal cell
dose response
drug mechanism
Drug Descriptors:
***gamma glutamyltransferase**
*glutathione
***acivicin**
*bromohydroquinone
*s (2 chloroethyl)cysteine
*s (2 chloroethyl)glutathione

```
     *s (3,6 dioxo 1,4 cyclohexadienyl)glutathione
     glutathione derivative
     probenecid
     unclassified drug
RN   (gamma glutamyltransferase) 85876-02-4; (glutathione) 70-18-8; (
     acivicin) 42228-92-2; (probenecid) 57-66-9
CN   Acivicin

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RN   9046-27-9  REGISTRY
ED   Entered STN:  16 Nov 1984
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OTHER NAMES:
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CN   γ-Glutamyl peptidyltransferase
CN   γ-Glutamyl transpeptidase
CN   γ-Glutamyl transpeptidase-related enzyme
CN   γ-Glutamyltransferase
CN   γ-GPT
CN   γ-GT
CN   γ-GTP
CN   E.C. 2.3.2.2
CN   L-γ-Glutamyl transpeptidase
CN   L-γ-Glutamyltransferase
CN   L-Glutamyltransferase
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L8 ANSWER 1 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN
RN 676551-24-9 REGISTRY
ED Entered STN: 23 Apr 2004
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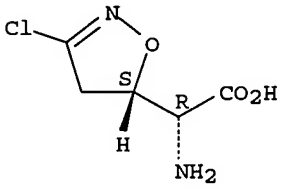

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L8 ANSWER 2 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN
RN 161922-40-3 REGISTRY
ED Entered STN: 04 Apr 1995
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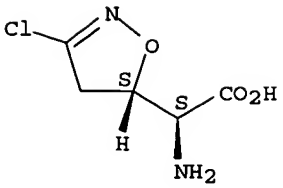

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ED Entered STN: 08 Nov 1986
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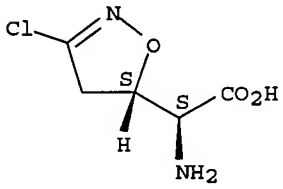
Relative stereochemistry.



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1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L8 ANSWER 4 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN
RN 104832-77-1 REGISTRY
ED Entered STN: 25 Oct 1986
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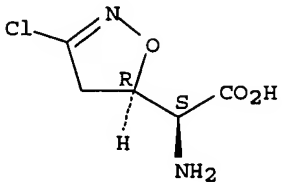

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RN 104832-76-0 REGISTRY
ED Entered STN: 25 Oct 1986
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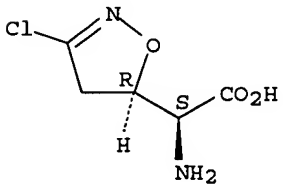
Relative stereochemistry.



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ED Entered STN: 16 Nov 1984
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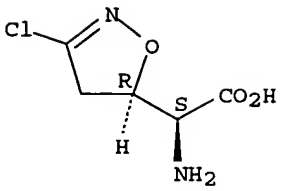

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L8 ANSWER 7 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN
RN 76898-56-1 REGISTRY
ED Entered STN: 16 Nov 1984
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(9CI) (CA INDEX NAME)
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(R*,R*)-(±)-
OTHER NAMES:
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FS STEREOSEARCH
MF **C5 H7 Cl N2 O3**
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LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, TOXCENTER, USPATFULL
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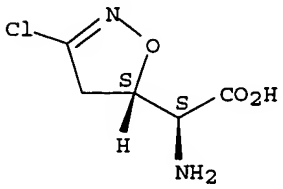
Relative stereochemistry.



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L8 ANSWER 8 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN
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ED Entered STN: 16 Nov 1984
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INDEX NAME)
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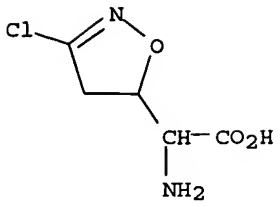

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L8 ANSWER 9 OF 9 REGISTRY COPYRIGHT 2005 ACS on STN
RN 42228-92-2 REGISTRY
ED Entered STN: 16 Nov 1984
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OTHER NAMES:
CN (α-S, 5S)-α-Amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid
CN Acivicin
CN Antibiotic AT 125
CN AT 125
CN NSC 163501
CN U 42126
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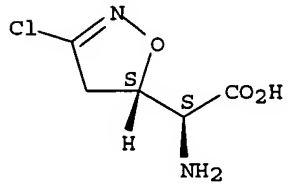
Absolute stereochemistry.



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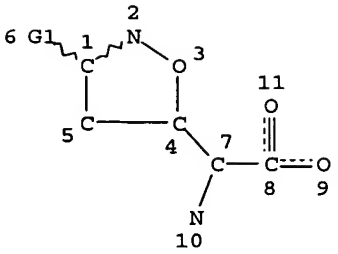

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L30 ANSWER 21 OF 51 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN DUPLICATE 1

ACCESSION NUMBER: 2002-20395 DRUGU T P B

TITLE: Transmembrane proteases as disease markers and targets for therapy.

AUTHOR: Antczak C; de Meester I; Bauvois B

CORPORATE SOURCE: INSERM; Inst.Curie; CNRS; Univ.Antwerp

LOCATION: Paris, Fr.; Wilrijk, Belg.

SOURCE: J.Biol.Regul.Homeostatic Agents (15, No. 2, 130-39, 2001) 1 Fig. 3 Tab. 101 Ref.

CODEN: JBRAER ISSN: 0393-974X

AVAIL. OF DOC.: Unite 365 INSERM, Institut Curie, 26 Rue d'Ulm, 75231 Paris Cedex 05, France. (email: brigitte.bauvois@curie.fr). (B.B.).

LANGUAGE: English

DOCUMENT TYPE: Journal

FIELD AVAIL.: AB; LA; CT

FILE SEGMENT: Literature

ABEX TMP are found in many normal and abnormal cells, and include neutral endopeptidase, ACE, aminopeptidase-N, aminopeptidase-A, dipeptidyl peptidase IV and gamma-glutamyl transpeptidase. Inhibitors include phosphoramidon, thiorphan, retrothiorphan, omaprilat, Z-13752A, SA-7060, captopril, enalapril, fosinopril, fasidotril, lisinopril, moexipril, quinapril, ramipril, trandolapril, actinonin, amastatin, ubenimex, probestin, PC-18, EC-27, EC-33, **acivicin** and anthglutin. Clinically inhibitors can reduce hypertension, **diabetic nephropathy** and tumor growth; in animals inhibitors can affect tumors, cardiovascular system, immunity and nervous tissue; in-vitro inhibitors affect apoptosis, immunity and cell function. Systemic administration of inhibitors may cause toxicity; some are not specific to abnormal tissue. Inhibitors are needed that are not toxic, are highly specific and can be delivered locally to the disease site. An example of this is ADEPT, where a fusion protein of CD20 antibody and beta-glucuronidase activates the doxorubicin glucuronide prodrug in Daudi lymphoma cells. (YC)

CT [02] NEOPLASM *TR; ANIMAL-NEOPLASM *OC; HYPERTENSION *TR; DIABETIC *TR; NEPHROPATHY *TR; VASCULAR-DISEASE *TR; PHOSPHORAMIDON *PH; THIORPHAN *PH; RETROTHIORPHAN *PH; OMAPRILAT *PH; Z-13752A *PH; SA-7060 *PH; CAPTOPRIL *PH; ENALAPRIL *PH; FOSINOPRIL *PH; FASIDOTRIL *PH; LISINOPRIL *PH; MOEXIPRIL *PH; QUINAPRIL *PH; RAMIPRIL *PH; TRANDOLAPRIL *PH; ACTINONIN *PH; AMASTATIN *PH; UBENIMEX *PH; PROBESTIN *PH; PC-18 *PH; EC-27 *PH; EC-33 *PH; **ACIVICIN** *PH; ANTHGLUTIN *PH; DOXORUBICIN *PH; EC-3.4.24.11 *FT; EC-3.4.15.1 *FT; EC-3.4.11.2 *FT; EC-3.4.11.7 *FT; EC-3.4.14.5 *FT; EC-2.3.2.2 *FT; IMMUNITY *FT; HEART *FT; VESSEL *FT; KIDNEY *FT; TUMOR-CELL *FT; CYTOSTATIC *FT; HYPOTENSIVE *FT; KIDNEY-BRUSH-BORDER-NEUTRAL-PROTEINASE *FT; NEPRILYSIN *FT; NEUTRAL-ENDOPEPTIDASE *FT; DIPEPTIDYL-CARBOXYPEPTIDASE *FT; ACE *FT; AMINOPEPTIDASE *FT; ASPARTATE-AMINOPEPTIDASE *FT; DIPEPTIDYL-PEPTIDASE-IV *FT; GAMMA-GLUTAMYLTRANSFERASE *FT; TISSUE-CULTURE *FT; TR *FT; PH *FT

(Table 1). As compared to the corresponding Mpv17+/+ kidneys, no significant difference in glutathione levels and in the activities of superoxide dismutase (SOD), catalase, GSSG reductase and glutathione transferase (GST) was observed in the kidneys of both mouse strains. However, in kidneys of Mpv17-/- mice γ-glutamyl transpeptidase (γ–GT) activity was increased by about two-fold, whereas glutathione peroxidase (GPx) activity was decreased by about one-third as compared to Mpv17+/+ animals. The following table illustrates the results:

TABLE 1 Enzyme activities in kidneys of Mpv17 -/- and Mpv17+/+ 7 - 9 months old mice

	Mpv17 -/-	Mpv17 +/+
	mmol/g of kidney wet weight	
GSH	2.19 ± 0.28 (93) [a)]	2.35 ± 0.35
	U / mg of protein	
Superoxide Dismutase	17.1 ± 1.6 (102)	16.7 ± 0.8
Catalase	381 ± 25 (88)	431 ± 16
	nmol/min per mg of protein	
Glutathione Peroxidase	176 ± 12 (68)	259 ± 16
GSSG Reductase	98 ± 10 (85)	115 ± 10
Glutathione Transferase	508 ± 52 (98)	520 ± 36
γ - Glutamyl Transpeptidase	2,330 ± 295 (197)	1,180 ± 70

Data are given as means ± SEM (n= 10 animals) [a)] % of Mpv17+/+

Example 4: Mpv17 dependent activities of γ-glutamyl transpeptidase and glutathione peroxidase in fibroblasts

Changes of enzyme activities determined in kidneys of Mpv17-/- mice were similarly observed when in cultured Mpv17-/- (LUSVX) cells were compared to Mpv17 expressing (NIX15) cells (Table 2). Most prominently, in Mpv17-/- cells the activities of γ–GT were elevated by about six-fold, whereas the activities of GPx were lowered by one-third. The similarity in the change of γ–GT and GPx activity measured in Mpv17+/+ and Mpv17-/- kidney and fibroblast culture suggests that these alterations occur at the cellular rather than the organismal level. The following table summarizes the results:

TABLE 2 Enzyme activities in LUSVX and NIX15 fibroblasts

	LUSVX (Mpv17 negative)		NIX15 (Mpv17 expressing)
	U/ mg of protein		
Superoxide Dismutase (n=2)	10.7	(61) [a)]	17.6
Catalase	410 ± 60	(87)	470 ± 90
	nmol/min per mg of protein		
Glutathione Peroxidase	53 ± 5	(66)	80 ± 7
γ-Glutamyl Transpeptidase	15 ± 0.4	(600)	2.5 ± 0.01

Data are given as means ± SEM (n=3-4) [a)] % of NIX15

Example 5: Mpv17 dependent changes in mRNA expression in fibroblasts

mRNA levels of the γ–GT and GPx genes were examined by quantitative RT-PCR in Mpv17expressing (NIX15) and Mpv17-/- (LUSVX) cells respectively (see Figure 2A below). γ–GT specific mRNA was enhanced by about 2-fold in Mpv17-/- cells. The expression of cellular GPx (cGPx), plasma GPx (pGPx), phospholipid hydroperoxide GPx (PHGPx) and of the nonselenium dependent GPx (nsGPx) was investigated. In Mpv17-/- cells only pGPx expression was decreased by about 80% (Figure 2A), which is basically consistent with the alteration in the activity of GPx (see Tables 1 and 2 above). Predominantly, pGPx appears to account for the overall low GPx activity. Remarkably, the expression of PHGPx, an enzyme responsible for protection from phospholipid peroxidation (R. L. Maser, B. S. Magenheimer and J. P. Calvet (1994), *Journal of Biological Chemistry*, **269**, pp. 27066-27073), was unaffected on the mRNA level.

The three different mouse SOD genes (CuZnSOD, MnSOD, ecSOD) show lower expression in Mpv17-/- cells, consistent with the lower SOD activity measured (see Table 2 above). No significant difference of xanthine dehydrogenase/ xanthine oxidase (XO) was detected on the mRNA level between Mpv17expressing and Mpv17 nonexpressing cells (see Figure 2A).

Example 6: Inhibition of γ-glutamyl transpeptidase activity restores glutathione peroxidase activity in Mpv17-/- cells

An inverse regulation of the glutathione-utilizing enzyme activities γ–GT and GPx was observed in Mpv17-/- animals and cells (see Tables 1 and 2 above). Because Mpv17-/- cells produce increased superoxide, a presumed regulatory function of the superoxide anion was tested by growing Mpv17-/- cells (LUSVX) in the presence of the SOD mimic MnTBAP (Y. Noda, M. Kohno, A. Mori and L. Packer (1999), *Journal Biological Chemistry*, **269**, pp. 23471-23476) Neither γ-GT nor GPx activities were changed significantly (Table 3) indicating that superoxide appears to have no role in the regulation of γ-GT and GPx in this system. Conversely, when Mpv17-/- cells were grown in the presence of acivicin, an efficient inhibitor of γ-GT, GPx activity was increased by about 1.6-fold. Thus, enzyme activities may be dependent on each

other in a way that γ–GT downregulates the activity of GPx. This inverse effect was also detected at the level of stable mRNA, as γ–GT inhibition led to a significant increase of pGPx and SOD mRNA levels (see Figure 2B).

TABLE 3 Activity of glutathione peroxidase and γ-glutamyl transpeptidase in Mpv17 -/- cells (LUSVX) in presence of MnTBAP or acivicin

	LUSVX	LUSVX + MnTBAP	LUSVX	LUSVX + acivicin
		nmol/min per mg of protein		
Glutathione Peroxidase	25.0 ± 1.0	26.1 v 0.6 (104%) [a)]	33.1 ± 1.3	53.5 ± 2.0 (162%)
γ-Glutamyl Transpeptidase	0.99 ± 0.02	0.94 ± 0.03 (95%)	0.96 ± 0.02	not detectable

Values are given as means ± SEM (n=3) [a)] % of controls

Example 7: Regulation of γ-GT and pGPx expression

The examples as documented herein above illustrate the following:

a) Reactive oxygen species in Mpv17 -/- cells

Using the ESR method superoxide was detected as the ROS species released from Mpv17 -/- fibroblasts. Production and secretion of superoxide are lower in Mpv17 expessing as compared to nonexpressing Mpv17-/- cells. These data are in line with the significance of ROS in the generation of glomerular injury (R. J. Johnson, D. Lovett, R. I. Lehrer, W. G. Couser and S. J. Klebanoff (1994), *Kidney International*,

45, pp. 352-359) and with an analysis of Mpv17-/- kidneys and isolated glomeruli, in which antioxidants were successfully used for therapeutic intervention in Mpv17-/- animals (C. J. Binder, H. Weiher, M. Exner and D. Kerjaschki (1999), *American Journal of Pathology*, **154**, pp. 1067-1075).

b) Activity and expression of oxidative enzymes

Activity and expression of enzymes involved in ROS and glutathione metabolism were determined in Mpv17-/- mice kidneys and fibroblasts in culture. An increase in γ–GT activity and a decrease in GPx activity were observed in both, Mpv17-/- kidneys and fibroblasts. In addition, a decrease in SOD activity was observed in Mpv17-/- fibroblasts. At the mRNA level, a negative correlation between the expression of γ–GT and the expression of the GPx and the SOD genes was observed in Mpv17-/- cells. All the three different SOD mRNAs tested were significantly decreased, but only the plasma GPx gene expression was strongly diminished, the latter presumably accounting for the decrease of GPx activity measured.

Negative correlations between the activity and expression of γ–GT and of enzymes involved in GSH and ROS metabolism have been reported earlier. Thus, inverse changes of GPx and γ-GT activities under the condition of oxidative stress were determined in rats exposed to cigarette smoke (C. V. Anand, U. Anand and R. Agarwal (1996), *Indian Journal Experimental Biology*, **34**, pp. 486-488) and in fetal mice exposed to alcohol (S. A. Amini, R. H. Dunstan, P. R. Dunkley and R. N. Murdoch (1996), *Free Radical Biology and Medicine*, **21**, pp. 357-365). Similarly, an inverse relationship of γ–GT and CuZnSOD expression has been noted recently in rat livers after iron poisoning (N. Taniguchi and Y. Ikeda (1998), *Advances in Enzymology and Related Areas of Molecular Biology*, **72**, pp. 239-278) But, in contrast to these previously described models, in the Mpv17 mouse model no chemical insult was applied.

c) Regulation of γ-GT and pGPx expression

In the absence of Mpv17 protein the γ–GT gene is upregulated while the mRNA level of pGPx is decreased. The mouse γ-GT gene is a single copy gene underlying intricate contol mechanisms involving at least seven promoters (N. Taniguchi and Y. Ikeda (1998), *Advances in Enzymology and Related Areas of Molecular Biology*, **72**, pp. 239-278). The membrane-bound γ–GT is involved in regulating cellular redox potential and intracellular GSH levels (T. C. Nichols, J. M. Guthridge, D. R. Karp, H. Molina, D. R. Fletcher and V. M. Holers (1998), *European Journal of Immunology*, **28**, pp. 4123-4129). The activity of γ–GT can be increased by glutathione depletion (R. J. van Klaveren, P. H. Hoet, J. L. Pype, M. Demedts and B. Nemery (1997), *Free Radical Biologoy and Medicine*, **22**, pp. 525-534) or by hyperoxia (A. Kugelman, H. A. Choy, R. Liu, M. M. Shi, E. Gozal and H. J. Forman (1994), *American Journal Respiratory Cell and Molecular Biology*, **11**, pp. 586-592) in different systems.

pGPx is an extracellular peroxidase of the selenium-containing GPx family, using GSH as well as and thioredoxin and glutaredoxin as thiol substrates (M. Björnstedt, J. Xue, W. Huang, B. Akesson and A. Holmgren (1994), *Journal of Biological Chemistry*, **269**, pp. 29382-29384). More abundant in kidney than in other tissues, pGPx is synthesized and secreted in the proximal tubules and in the glomeruli, consistent with its function in protecting kidney from extracellular oxidative damage (R. L. Maser, B. S. Magenheimer and J. P. Calvet (1994), *Journal of Biological Chemistry*, **326**, pp. 579-585; D. M. Tham, J. C. Whitin, K. K. Kim, S. X. Zhu and H. J. Cohen (1998), *American Journal of Physiology*, **275**, G1463-1471). Downregulation of pGPx as observed in Mpv17-/- cells weakens the protection against extracellular oxidative insult.

The γ–GT activity in Mpv17-/- cells controls the level of pGPx mRNA as γ–GT inhibition relieves this downregulation (Fig2b). This control might involve imbalanced levels of intra- or extracellular GSH or superoxide due to enhanced γ–GT activity, presumably mediated by the activation of superoxide responsive transcription factors such as NF-κB or AP-1 (H. L. Pahl and P. A. Baeuerle (1994), *Bioessays*, **16**, pp.

497-502). However, superoxide removal does neither affect the γ–GT nor the GPx activity, arguing against superoxide as a regulator.

Several genes relevant to the development of the disease phenotype, i.e. MMP-2 and its regulator TIMP-2, have been shown to be upregulated in Mpv17-/- mice earlier (A. Reuter, A. Nestl, R. M. Zwacka, J. Tuckerman, R. Waldherr, E. M. Wagner, M. Hoyhtya. A. M. Meyer zum Gottesberge, P. Angel and H. Weiher (1998), *Molecular Biology of the Cell*, **9**, pp. 1675-1682). Since antioxidant intervention is effective in phenotype prevention in our model (C. J. Binder, H. Weiher, M. Exner and D. Kerjaschki (1999), *American Journal of Pathology*, **154**, pp. 1067-1075), these alterations should be consequences rather than causes to ROS generation. By contrast, the data presented here suggest that overproduction of γ-GT in these animals is causal to elevated ROS levels (see below).

d) Origin of enhanced ROS levels in Mpv17 -/- mice

Enzymes most affected in Mpv17-/- kidneys and cells, γ–GT and pGPx, both exert their enzymatic activity predominantly in the extracellular space. In particular, γ-GT expression and activity are enhanced in the absence of the Mpv17 function. Cells overproducing γ-GT should be efficiently protected against intracellular oxidative injury by increased supply of intracellular GSH. Extracellular GSH is metabolised by γ-GT to glutamate and cysteinylglycine which in contrast to GSH can directly enter cells and thus provide them with a source of cysteine (M. W. Lieberman, A. L. Wiseman, Z. Z. Shi, B. Z. Carter, R. Barrios, C. N. Ou, P. Chevez-Barrios, Y. Wang, G. M. Habib, J. C. Goodman, S. L. Huang, R. M. Lebovitz and M. M. Matzuk (1996), *Proceedings of the National Academy of Sciences of the U.S.A.*, **76**, pp. 5606-5610). The latter is present at lowest concentration of all amino acids and a limiting component for intracellular de novo GSH synthesis. Thus, γ-GT, localized at the luminal surface of the renal proximal tubules, plays a key role in cysteine and glutathione homeostasis in maintaining cellular GSH levels (A. Kugelman, H. A. Choy, R. Liu, M. N. Shi, E. Gozal and H. J. Forman (1994), *American Journal Respiratory Cell and Molecular Biology*, **11**, pp. 586-592).

At the same time, increased γ-GT activity might lead to a depletion of extracellular GSH and thereby weaken the resistance against extracellular ROS. In mice, however, this is unlikely, because plasma GSH levels are about 100-fold higher than in humans (O. W. Griffith and A. Meister (1979), *Prodeedings of the National Academy of Sciences of the U.S.A.*, **76**, pp. 5606-5610), that is well above a critical substrate concentration for pGPx activity of <0.5 μM (A. Wendel and P. Cikryt (1980), *FEBS Letters*, **120**, pp. 209-211). Instead, increased γ–GT activity may directly enhance superoxide in the Mpv17-/- system. Such direct production of superoxide by γ-GT activity was recently demonstrated in an in vitro system containing GSH and transferrin as an iron source. It was shown that superoxide was generated by the reaction of the GSH breakdown product cysteinylglycine (R. Drozdz, C. Parmentier, H. Hachad, P. Leroy, G. Siest and M. Wellman (1998), *Free Radicals Biology and Medicine*, **25**, pp. 786-792). Superoxide can instantly undergo a Fenton type reaction to turn into the highly noxic hydroxyl radical, causing lipid- and protein peroxidation (R. Drozdz, C. Parmentier, H. Hachad, P. Leroy, G. Siest and M. Wellman (1998), *Free Radicals Biology and Medicine*, **25**, pp. 786-792). In vivo, hydroxyl radical generation and lipid peroxidation in the presence of metals and under conditions of enhanced γ–GT activity have been described earlier in rat liver (K. E. Brown, M. T. Kinter, T. D. Oberley and D. R. Spitz (1998), *Free Radical Biology and Medicine*, **24**, pp. 545-555; A. A. Stark, E. Zeiger, D. A. Pagano (1993) *Carcinogenesis*, **14**, pp. 183-189; A. Paolicchi, R. Tongiani, P. Tonarelli, M. Comporti and A. Pompella (1997), *Free Radicals Biology and Medicine*, **22**, pp. 853-860).

The above described experiments clearly demonstrate that γ–GT activity plays a key role in the generation of extracellular ROS. Recently, γ–GT upregulation has been reported to be causal to oxidation damage during short-term ischemia of rat kidney and this effect was inhibitable by acivicin (J. C. Cutrin, B. Zingaro, S. Camandola, A. Boveris, A. Pompella and G. Poli (2000), *Kidney International*, **57**, pp. 526-533). Thus, the use of γ–GT inhibitors provides a potent and useful treatment of ROS degenerated diseases and injuries in humans as well.

Mpv 17-/-mice, i.e. mice of the glomerulosclerosis reference strains are treated, in accordance with this invention, by oral administration of 5 to 50 mg/kg activicin (AT-125) for several weeks. The protective use of activicin is analyzed by pathological methods and/or molecular means.

Claims

1. Use of γ-GT inhibitors for the preparation of a pharmaceutical composition for the treatment of a degenerative disease.

2. The use of claim 1, wherein said degenerative disease is a chronic renal disease or an inner ear degenerative condition or injury.

3. The use of claim 2 wherein said chronic renal disease is ROS induced.

4. The use of claim 3, wherein said chronic renal disease is selected from the group consisting of focal glomerulosclerosis, segmental glomerulosclerosis, minimal change nephrosis, inflammatory glomerulopathies, diabetic nephropathy and autoimmuno glomerulopathies.

5. The use of claim 2, wherein said inner ear injury is ROS induced.

6. The use of claim 5, wherein said ROS induced inner ear injury is sensineural deafness induced by age, physiological status, metabolic status or drugs.

7. The use of claim 6, wherein said drugs are selected from aminoglycosides or cisplatin derivatives.

8. The use of claim 2, wherein said inner ear degenerative condition is otosclerosis.

9. The use of any one of claims 1 to 8, wherein said γ-GT inhibitor is selected from the group consisting of AT-125, Acivicin or its derivatives, γ-glutamyl amino acids and peptides of the general formula γ-Glu-XY, pepticles of the general formula (CysGlyX), peptidomimetic glutathion analogues, compounds or derivatives of the type L-2-amino-4-boronobutanoic acid (ABBA), and anilides, such as γ-glutamyl-7-amido-4-methylcoumarin (γ-Glu-AMC).

10. The use of claim 9, wherein X and Y stand for any naturally occurring aminoacid, a modified aminoacid, a oligopeptide or a polypeptide.

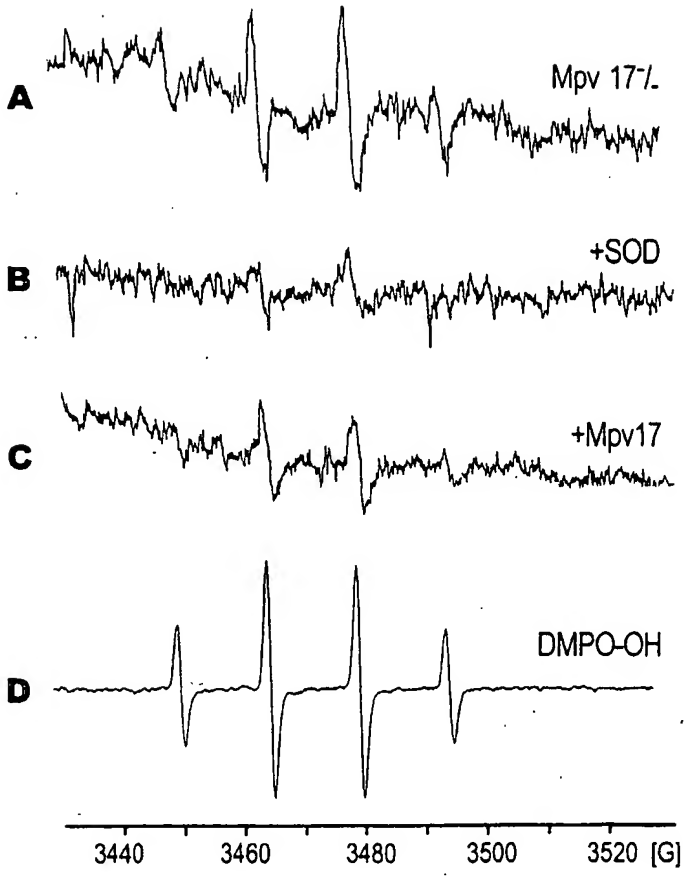
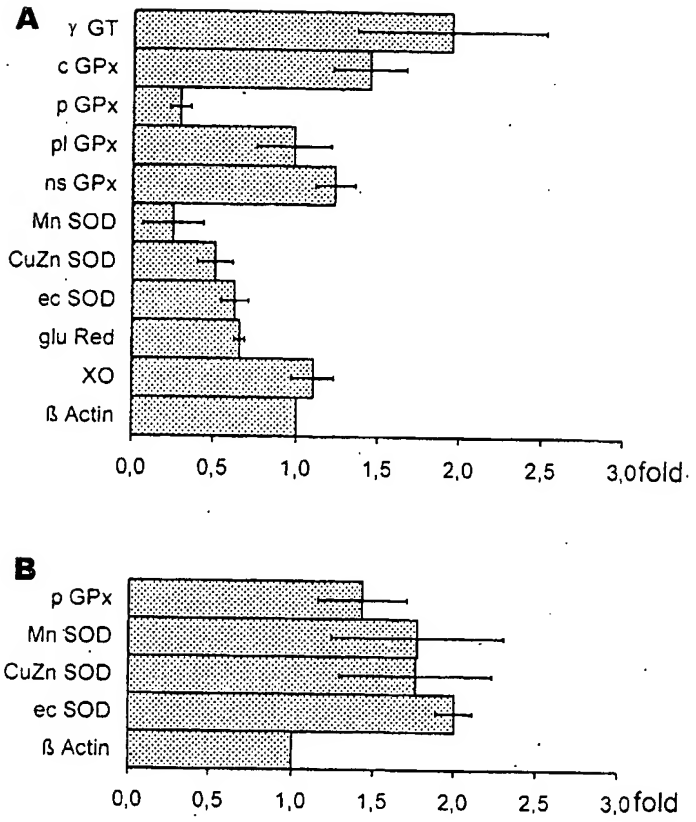


Fig. 1


A
γ GT
c GPx
p GPx
pl GPx
ns GPx
Mn SOD
CuZn SOD
ec SOD
glu Red
XO
ß Actin
0,0
0,5
1,0
1,5
2,0
2,5
3,0fold
B
p GPx
Mn SOD
CuZn SOD
ec SOD
ß Actin
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2,0
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Fig. 2

INTERNATIONAL SEARCH REPORT

Interna Application No
PCT/EP 02/01799

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/06 A61P27/16 A61P13/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 758 551 A (MEISTER ALTON ET AL) 19 July 1988 (1988-07-19) cited in the application abstract; claims column 3, line 47 - line 63 column 2, line 47 - line 55 --- -/--	1-4,9,10

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
27 June 2002	22/07/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Escolar Blasco, P

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INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/EP 02/01799

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

Interna Application No
PCT/EP 02/01799

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	EVANS P., HALLIWELL B: "Free radicals and hearing: cause, consequence and criteria" ANNALS OF THE NEW YOORK ACADEMY OF SCIENCES, 'Online! vol. 884, no. 1, 1999, pages 19-40, XP002203800 Retrieved from the Internet: <URL:www.annalsnyas.org> 'retrieved on 2002-06-27! "Interaction of drugs with reactive oxygen species" ---	1,2,5-7, 9
X	LOPEZ-GONZALEZ MIGUEL A ET AL: "Ototoxicity caused by cisplatin is ameliorated by melatonin and other antioxidants." JOURNAL OF PINEAL RESEARCH., vol. 28, no. 2, March 2000 (2000-03), pages 73-80, XP002203801 ISSN: 0742-3098 page 73 ---	1,2,5-7, 9
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Internat Application No
PCT/EP 02/01799

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4758551 A	19-07-1988	NONE	

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ACCESSION NUMBER: 2000:30048831 BIOTECHNO
TITLE: Bioartificial kidney for full renal replacement therapy
AUTHOR: Humes H.D.
CORPORATE SOURCE: Dr. H.D. Humes, Department of Internal Medicine, Univ. of Michigan Medical Center, Ann Arbor, MI 48109, United States.
E-mail: dhumes@umich.edu
SOURCE: Seminars in Nephrology, (2000), 20/1 (71-82), 79 reference(s)
CODEN: SNEPDJ ISSN: 0270-9295
DOCUMENT TYPE: Journal; General Review
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
CT *erythropoietin; *artificial kidney; ***chronic kidney disease**; *acute kidney failure; ouabain; phlorizin; 4 aminohippuric acid; **acivicin**; colecalciferol; parathyroid hormone; probenecid; gene therapy; genetic engineering; mortality; morbidity; blood filter; continuous ambulatory peritoneal dialysis; hemofiltration; kidney tubule absorption; ammonia formation; biosensor; human; review; priority journal
RN (erythropoietin) 11096-26-7; (ouabain) 11018-89-6, 630-60-4; (phlorizin) 60-81-1, 7061-54-3; (4 aminohippuric acid) 61-78-9; (**acivicin**) **42228-92-2**; (colecalciferol) 1406-16-2, 67-97-0; (parathyroid hormone) 12584-96-2, 68893-82-3, 9002-64-6; (probenecid) 57-66-9